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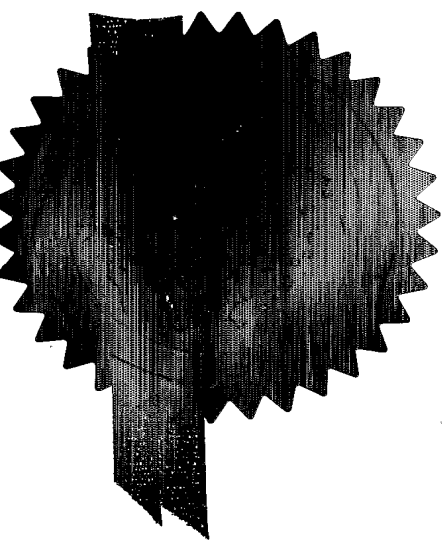

Signed Stephen Hordley

Dated 15 March 2005

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Patents Form 1/77

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Request for grant of a patent

(See the notes on the back of this form. You can also get an explanatory leaflet from the Patent Office to help you fill in this form)

1. Your reference — SCB/NLW/P71002GB00

19FEB04 E874427-1 D02882
P01/7700 0.00-0403635.6 NONE

2. Patent application number *(The Patent Office will fill this part in)* — 0403635.6 ✓ — 18 FEB 2004 ✓

3. Full name, address and postcode of the or of each applicant *(underline all surnames)*

Devgen NV
Technologiepark 9
B-9052 Zwijnaarde
Belgium

Patents ADP number *(if you know it)* 7902299001

If the applicant is a corporate body, give the country/state of its incorporation — Belgium

4. Title of the invention — Pyridinocarboxamides with improved activity as kinase inhibitors

5. Name of your agent *(if you have one)* — BOULT WADE TENNANT

"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*

VERULAM GARDENS
70 GRAY'S INN ROAD
LONDON
WC1X 8BT

Patents ADP number *(if you know it)* — 42001 ✓

6. Priority: Complete this section if you are declaring priority from one or more earlier patent applications, filed in the last 12 months.

Country	Priority application number *(if you know it)*	Date of filing *(day / month / year)*

7. Divisionals, etc: Complete this section only if this application is a divisional application or resulted from an entitlement dispute (see note f)

Number of earlier UK application	Date of filing *(day / month / year)*

8. Is a Patents Form 7/77 (Statement of inventorship and of right to grant of a patent) required in support of this request? — Yes

Answer YES if:

a) any applicant named in part 3 is not an inventor, or
b) there is an inventor who is not named as an applicant, or
c) any named applicant is a corporate body.

Otherwise answer NO (See note d)

Patents Form 1/77

9) Enter the number of sheets for any of the following items you are filing with this form. Do not count copies of the same document

Continuation sheets of this form	
Description	99
Claim *(s)*	2
Abstract	
Drawing *(s)*	1 & 1

10. If you are also filing any of the following, state how many against each item.

Priority documents	
Translations of priority documents	
Statement of inventorship and right to grant of a patent *(Patents Form 7/77)*	
Request for preliminary examination and search *(Patents Form 9/77)*	
Request for substantive examination *(Patents Form 10/77)*	
Any other documents *(please specify)*	

11. I/We request the grant of a patent on the basis of this application.

Signature: Bower Wade Tennent

Date: 18 February 2004

12. Name and daytime telephone number of person to contact in the United Kingdom: Nina White 020-7430-7500

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Notes

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Pyridinocarboxamides with improved activity as kinase inhibitors.

The present invention relates to improved pyridinocarboxamides, to methods for the preparation of such derivatives, to compositions containing such derivatives, and to uses of such derivatives.

In particular, the invention relates to pyridinocarboxamides that can be used to modulate the activity of enzymes and/or to modulate biological processes *in vitro* and/or *in vivo*, to pharmaceutical and/or veterinary compositions that contain such derivatives, and to pharmaceutical and/or veterinary uses of such derivatives.

More in particular, the invention relates to pyridinocarboxamides that can be used to modulate the activity of kinases *in vitro* and/or *in vivo*, and that as such can (also) be used to modulate the biological pathways and/or biological processes in which such kinases are involved. The pyridinocarboxamides of the invention can also be used for preventing and/or treating diseases or disorders in which such kinases, pathways and/or processes are involved.

Another aspect of the invention relates to the use of said pyridinocarboxamides in methods for the preparation of compositions, and in particular in methods for the preparation of pharmaceutical and/or veterinary compositions.

Other objects, aspects, embodiments, uses and advantages of the invention will become clear from the further description below.

It is known in the prior art that inhibitors of certain kinases can be used in the treatment of diabetes, obesity and other metabolic diseases. Some examples of such kinases include JNK1, p38 kinase, GSK-3, IKKbeta (IKappaB kinase beta) and p70S6K.

The art also describes that several isoforms of protein kinase C ("PKC") are associated with metabolic diseases such as diabetes and obesity. Reference is inter alia made to US-A-6.376.467, US-A-6.284.784, US-A-6.080.784, US-A- 6.057.440, US-A-5.962.504, WO 02/22709, WO 01/30331, WO 96/40894 and the further references cited therein.

As described in these references, there are currently 10 known isoforms of PKC, known as alpha, beta-I, beta-II, gamma, delta, epsilon, zeta, eta, iota/lambda and theta, respectively (Nishizuka, Science 258, 607-614 (1992); Selbie et al., J. Biol. Chem. 268,

24296-24302 (1993)). Based on sequence homology and biochemical properties, these PKC isozymes are generally subdivided into three groups:

(a) the group of "conventional" PKCs comprising the alpha, beta-I, beta-II and gamma isozymes, which are all regulated by calcium, diacylglycerol and phorbol esters;

(b) the group of "novel" PKCs comprising the delta, epsilon, theta and eta isozymes, are which are all calcium-independent, but diacylglycerol- and phorbol ester-sensitive; and

(c) the group of "atypical" PKCs, the zeta and iota/lambda isozymes, which are insensitive to calcium, diacylglycerol and phorbol 12-myristate 13-acetate.

A further subgroup may be comprised of PKC mu and protein kinase D (see for example US-A-6.376.467; Johannes et al, Biol. Chem. 269, 6140-6148 (1994); and Valverde et al, Proc. Natl. Acad. Sci. USA 91, 8572-8576 (1994)).

US-A-6.057.440, US-A-5.698.578 and US-A-5.739.322 describe the use of bis indolyl maleimide compounds as specific inhibitors of PKC beta in the prevention and treatment of diabetes and diabetes-related complications. These patent applications and patents also describe an assay that can be used to determine the specificity of a given inhibitor for one isoform of PKC compared to another (referred to in these patents as the "PKC Enzyme Assay").

The German patent application DE 197 40 384 A1 describes that antisense oligonucleotide sequences specific for certain PKC isoforms, and in particular against the alpha, delta, epsilon and zeta isoforms, may be used in the prevention or treatment of complications associated with diabetes.

WO 01/81633 describes the association on PKC zeta with diabetes. Similarly, WO 94/18328 describes that the "atypical" PKC isozyme iota is involved in diabetes.

The link between PKC epsilon and diabetes/obesity has been established in two model systems for diabetes and obesity, i.e. the sand rat *Psammomys* and the High Fat Fed Rat. Reference is *inter alia* made to Shafrir et al., Annals New York Academy of Sciences 892:223-241 (1999), Donelly and Qu, Clin. Exper. Pharmacol. And Phsyiol. 25: 79-87 (1998) and Qu et al., Journal of Endocrinology 162: 207-214 (1999). The latter two references also suggest that PKC theta may be involved in diabetes and obesity

WO 00/01805 describes PKC-epsilon knock out mice. This animal model is used to demonstrate that PKC epsilon can be used as a target for drugs to reduce anxiety, modulate alcohol consumption and drug abuse, addiction, withdrawal syndrome, muscle spasms, convulsive seizures, epilepsy and to modulate the action of drugs that target the GABA-A receptor.

WO 00/01415 and US-A-6.376.467 describe the use of inhibitors of PKC epsilon in the treatment of pain, in particular chronic hyperalgesia and/or inflammatory pain (reference is also made to WO 02/102232 and WO 03/89457). As examples of suitable inhibitors, both peptides as well as small molecules are mentioned. WO 97/15575 and WO 01/83449 describe modulators of PKC with specific binding activity with respect to PKC epsilon. Peptide inhibitors that provide isozyme-specific modulation of PKC (in particular of PKC gamma and PKC epsilon) are described in WO 03/089456 and WO 03/089457.

For the sequence of human PKC epsilon, reference is made inter alia made to Basta et al., Biochim. Biophys Acta, 1132 (1992), 154-160, as well as to SWISS-PROT entry Q02156 and EMBL entry X65293.

WO 03/04612 describes the use of inhibitors of PKC theta as an immunosuppressive agent (e.g. during organ transplant) and for treatment of systemic lupus erythematosus. Reference is also made to Castrillo et al., J. Exp. Med., 194, 9 (2001), p. 1231-1242, who describe that PKC epsilon plays a critical role as a mediator in signalling cascades of activated macrophages, and that the absence of PKC epsilon can compromise the successful initiation of an effective immune response against a range of bacterial pathogens.

US 2003/0134774 describes the use of inhibitors of PKC epsilon and PKC theta in inhibiting the onset of a cardiac disorder and the progression of heart failure.

For other potential uses of inhibitors of PKC and/or of specific isoforms of PKC, reference is for example made to US 2002/0164389, US 2003/0118529, US 2003/0176424, US 2003/0176423, US 2003/0166678, US 2003/0134774, US 2003/0166678, US 2003/0176424, US 2003/0199423, WO 03/82859, WO 02/103000 and WO 02/87417. Other potential applications will be clear to the skilled person.

Applicant's international application PCT/EP03/14674 entitled "*Kinase sequences useful for developing compounds for the prevention and/or treatment of metabolic diseases and nucleotide sequences encoding such kinase sequences*" (with a filing date of December 17, 2003 and invoking on the priorities of UK application 0230014.3 and US provisional application 60/436,380, both of December 23, 2002) describes four kinases - referred to as "*JIK*", "*PSK*", "*TAO1*" and "*Q9P2I6*", respectively) - that are potential targets in metabolic disease.

The compound (R)-(+)-*trans*-N-(4-pyridyl)-4-(1-aminoethyl)-cyclohexanecarboxamide (Example 24 below) is commercially available from CALBIOCHEM as an inhibitor of "*rhoA-dependent coiled coil serine/threonine kinase*" or "*ROCK*" (Compound Y-27632; Cat. No. 688000). Reference is also made to US patent 4,997,834 by Muro et al.; the European application EP 0 370 498 by Muro et al.; Chitaley et al., *Nat. Med.*, **7**, 119 (2001); Narumiya et al., *Methods Enzymol.*, **325**, 273 (2000), Davies et al., *Biochem. J.*, **351**, 95 (2000); Maekawa et al., *Science*, **285**, 895 (1999); Hirose et al., *J. Cell. Biol.*, **141**, 1625 (1999); Uehata et al., *Nature*, **389**, 990 (1997) and Sakamoto et al., *J.Pharmacol. Sci.*, **92**, 56 (2003).

However, the prior art does not disclose that this compound can be used to selectively inhibit the calcium-independent, but diacylglycerol- and phorbol ester-sensitive isoforms of PKC (as mentioned below), compared to other isoforms of PKC (as mentioned below).

It is a general object of the invention to provide compounds that can be used in the pharmaceutical and veterinary field, for example in the prevention and/or treatment of diseases and disorders in humans and/or animals.

It is a particular object of the invention to provide compounds that can be used in (the preparation of pharmaceutical compositions for) the treatment of metabolic diseases such as diabetes and obesity in humans.

It is another object of the invention to provide compounds that can be used to modulate, and in particular inhibit, the activity of kinases *in vitro* and/or *in vivo*.

It is a particular object of the invention to provide compounds that have improved specificity for PKC compared to other kinases.

More in particular, it is an object of the invention to provide compounds that have improved specificity for certain isoforms of PKC compared to other isoforms.

Even more in particular, it is an object of the invention to provide compounds that have improved specificity for the calcium-independent, but diacylglycerol- and phorbol ester-sensitive isoforms of PKC (such as the delta, epsilon, theta and eta isoforms) compared to the "conventional PKCs (i.e. the alpha, beta-I, beta-II and gamma isoforms) and the "atypical" PKCs (i.e. the zeta and iota/lambda isoforms).

Other objects, aspects, embodiments, uses and advantages of the invention will become clear from the further description below.

Generally, it has now been found that the above objectives can be achieved by compounds that have the following structural characteristics/features:

(1) a substituted (as defined below) or unsubstituted, saturated, unsaturated or aromatic 4-, 5-, 6-, 7- or 8-membered ring containing carbon atoms and at least one hydrogen-accepting hetero-atom and optionally 1 or 2 further hetero-atoms chosen from oxygen, sulfur and nitrogen, and in particular nitrogen (hereinbelow also referred to as "*Ring (1)*"), covalently bound to:

(2) the nitrogen atom of an amide bond $-NR_a-(C=O)-$ (hereinbelow also referred to as "*Amide group (2)*"), in which R_a is as defined below, and in which the carbon atom of the carbonyl-group $-(C=O)-$ is covalently bound to:

(3) a substituted (as defined below) or unsubstituted, saturated, unsaturated or aromatic 4-, 5-, 6-, 7- or 8-membered ring containing carbon atoms optionally 1 or 2 hetero-atoms chosen from nitrogen, oxygen and sulfur (hereinbelow also referred to as "*Ring (3)*"); which is bound to:

(4) an alkylene amino group of the formula $-(CR_1R_2)_n-NR_bR_c$, in which n is 0, 1 or 2, and most preferably 1 or 2, R_1 and R_2 are as defined below, and R_b and R_c are such that the amino group $-NR_bR_c$ it is essentially in a protonated form (as defined below) at a pH in the range of 5.0 – 9.0 , preferably 6.0 – 8.0 , such as about pH 7.0 (determined as described below), and in which R_b and R_c may in particular be as further defined below (*hereinbelow also referred to as "Alkylene aminogroup (4)*"); and in which:

(5) the distance between the at least one hydrogen-accepting hetero atom in Ring (1) and the nitrogen atom of the amino group in the Alkylene aminogroup (4), as determined

using a Scatter Plot (generated as indicated above) (as further described below), is in the range of 11.0 to 11.8, preferably from 11.0 to 11.6 and more preferably in the range of 11.0 to 11.4 Angstrom.

These compounds will be generally referred to herein as "*compounds of the invention*"

In the compounds of the invention, besides the at least one hydrogen-accepting hetero-atom, the Ring (1) may optionally contain 2 and preferably only 1 hetero atom(s) chosen from nitrogen, oxygen and/or sulfur atoms, which 1 or 2 heteroatom(s) are preferably nitrogen. Most preferably, however, the Ring (1) contains only carbon atoms and the at least one hydrogen-accepting hetero-atom, and thus no further hetero-atoms.

In the compounds of the invention, the Ring (1) may be saturated, unsaturated (i.e. containing 1 or 2 double bonds) or aromatic, and is most preferably aromatic.

In the compounds of the invention, the at least one hydrogen-accepting hetero-atom in the Ring (1) is most preferably a nitrogen atom.

In the compounds of the invention, the Ring (1) is preferably a 5- or 6-membered ring, and preferably a 6-membered ring. Even more preferably, Ring (1) is a 5- or 6-membered ring, and preferably a 6-membered ring, that contains carbon atoms and one hydrogen-accepting hetero-atom and optionally contains 1 further hetero-atom chosen from oxygen, sulfur and nitrogen, and preferably nitrogen. Most preferably, Ring (1) is a 5- or 6-membered ring, and preferably a 6-membered ring, that contains carbon atoms and the one hydrogen-accepting hetero-atom, and no further hetero-atoms.

In the compounds of the invention, when the Ring (1) is a 5-membered ring, the at least one hydrogen-accepting hetero-atom is in preferably the 2- or the 3-position relative to the carbon atom of Ring (1) that is covalently bound to the Amide group (2).

In the compounds of the invention, when the Ring (1) is a 6-membered ring, the at least one hydrogen-accepting hetero-atom is preferably in the 2-, 3- or 4-position relative to the carbon atom of Ring (1) that is covalently bound to the Amide group (2), and most preferably in the (4)-position.

In the compounds of the invention, the Ring (1) may be unsubstituted or may be substituted with 1-4, and preferably 1 or 2, substituents that are each independently and suitably chosen from the group consisting of halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy,

substituted or unsubstituted aryl, cyano, nitro, hydroxy and an amino group NR_dR_e (in which R_d and R_e may each independently be one of the groups mentioned for R_b and R_c hereinbelow (including the ring structures), but may in addition also each independently be substituted or unsubstituted aryl). Preferably, the Ring (1) is unsubstituted or is substituted with 1 or 2, and preferably only 1, such substituent(s). These possible substituents on Ring (1) are also generally indicated in the formulas below with "X", it being understood that, in accordance with the foregoing, 0 or 1-4, and preferably 0, 1 or 2, and most preferably 0 or 1, such substituents may be present, in which each time such a substituent is present, it may be independently and suitably chosen from the group mentioned above, and it may be present on any suitable position of the ring.

According to one possible, but less preferred embodiment, the Ring (1) may be substituted with a hydrogen-donating substituent, such as –OH, -SH or most preferably an amino group $-NHR_d$ (in which R_d is as defined below, and is preferably an substituted or unsubstituted aryl group). This substituent is preferably present on the carbon atom next to the hydrogen-accepting hetero atom (and when the Ring (1) is fixed with an additional Ring (7) as defined below, on the carbon atom next to the hydrogen-accepting hetero atom that is farthest removed (in terms of number of carbon atoms that lie between) from the position that the Ring (7) is attached to Ring (1).

Some preferred, but non-limiting examples of groups that may be present as Ring (1) in the compounds of the invention are: 4-pyridyl; substituted 4-pyridyl such as2-methyl-4-pyridyl, 3-methyl-4-pyridyl, etc.; and also for example 2-arylamino-4-pyridyl.

According to a specific, but non-limiting, embodiment of the compounds of the invention, the Ring (1) carries 2 substituents on adjacent carbon atoms of Ring (1), which substituents, together with the two carbon atoms of Ring (1) to which they are bound, form:

(6) a substituted (as defined below) or unsubstituted, saturated, unsaturated or aromatic 4-, 5-, 6- or 7-membered ring that contains carbon atoms and at least one hydrogen donating group -(NH)- and optionally one further hetero atom chosen from oxygen, sulfur and nitrogen, and most preferably nitrogen, that is fused to Ring (1) (hereinbelow also referred to as "*Ring (6)*").

In the compounds of the invention, when a Ring (6) is present, the Ring (6) is preferably a 5- or 6- membered ring, and most preferably a 5 membered ring.

In the compounds of the invention, when a Ring (6) is present, the Ring (6) is preferably contains only carbon atoms and the at least one hydrogen-donating group.

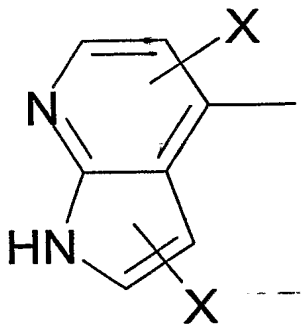
In the compounds of the invention, when a Ring (6) is present, the Ring (6) may be saturated, contain 1 or 2 unsaturated bonds or be aromatic, and is preferably aromatic.

In the compounds of the invention, when a Ring (6) is present, the distance between the at least one hydrogen-accepting hetero atom in Ring (1) and the nitrogen atom of the at least one hydrogen donating group in Ring (6) is preferably in the range of 2.30 to 2.50 Angstrom, more preferably in the range of 2.30 to 2.45 Angstrom and most preferably in the a range of 2.30 to 2.40 Angstrom. For example, in the group indicated by the formula directly below, this distance (as determined by molecular modelling using a suitable computer algorithm) is about 2.39 Angstrom, whereas in the corresponding unsaturated 5-membered ring, it is about 2.34 Angstrom, and in the corresponding unsaturated 6 membered ring, it is about 2.35 Angstrom. For a free mono-C_1-C_6alkyl amino group in the corresponding position (which is less preferred in the invention), this distance will be about 2.43 Angstrom

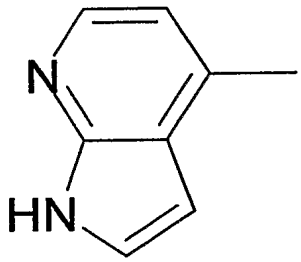
In the compounds of the invention, the Ring (6) may be substituted with 1 or 2, and preferably 1, substituent(s) that are each independently and suitably chosen from the group consisting of halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, substituted or unsubstituted aryl, nitro, hydroxy and an amino group NR_dR_e (in which R_d and R_e are as defined herein), but is preferably unsubstituted. These possible substituents on Ring (6) are also generally indicated in the formula's below with "X", it being understood that, in accordance with the foregoing, 0, 1 or 2, and preferably 0 or 1, such substituents may be present, in which each time such a substituent is present, it may be independently and suitably chosen from the group mentioned above, and it may be present on any suitable position of the ring.

Some specific, but non-limiting examples of groups that may be present as the fused bicyclic nucleus formed by Ring (1) and Ring (6) are:

a) a group

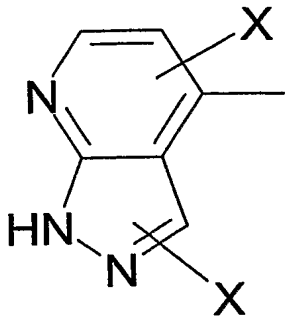


which represents a 7-azaindole group

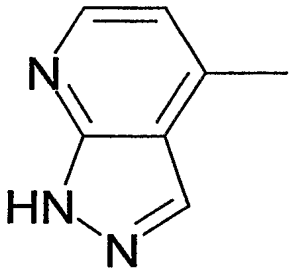


that is unsubstituted (X=H) or that be may be substituted, i.e. independently on any one of the rings or on both rings, with 1 or 2 substituents X, in which said 1 or 2 substituents X are independently and suitably chosen from the substituents X as mentioned for Ring (1) and for Ring (6), respectively, hereinabove.

b) a group

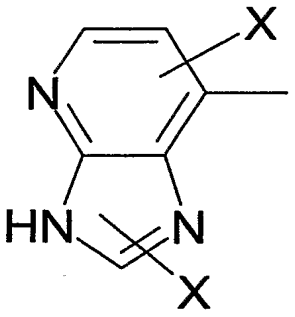


which represents a group

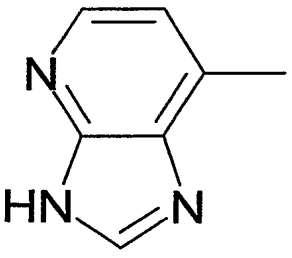


that is unsubstituted (X=H) or that be may be substituted, i.e. independently on any one of the rings or on both rings, with 1 or 2 substituents X, in which said 1 or 2 substituents X are independently and suitably chosen from the substituents X as mentioned for Ring (1) and for Ring (6), respectively, hereinabove.

c) a group



which represents a group



that is unsubstituted (X=H) or that be may be substituted, i.e. independently on any one of the rings or on both rings, with 1 or 2 substituents X, in which said 1 or 2 substituents X are independently and suitably chosen from the substituents X as mentioned for Ring (1) and for Ring (6), respectively, hereinabove.

In the compounds of the invention, the Amide group (2) may have the *cis*-configuration or the *trans*-configuration, with the *cis*-configuration being particularly preferred.

It will also be clear to the skilled person that the Amide group (2) may be in the form of different tautomers, and all these possible tautomers are encompassed within the scope of the invention.

Also, although in the compounds of the invention the Amide group (2) is most preferably bound with its nitrogen atom to Ring (1) and with its carbon atom to Ring (3), it is not excluded, but less preferred, that the Amide group (2) is bound with its carbon atom to Ring (1) and with its nitrogen atom to Ring (3), as for example shown in the compound of Example 18 below.

In the compounds of the invention, the group R_a may be hydrogen or may be linear or branched, substituted or unsubstituted C_1-C_6 alkyl, substituted or unsubstituted C1-C6 alkoxy or substituted or unsubstituted aryl, and is preferably hydrogen, methyl or ethyl, with methyl and hydrogen being particularly preferred.

Alternatively, the group R_a, the nitrogen atom of the Amide group (2) to which said group R_a is bound, the carbon atom of Ring (1) to which the nitrogen atom of the Amide group (2) is bound, and one carbon atom of Ring (1) adjacent to the carbon atom of Ring (1) to which the nitrogen atom of the Amide group (2) is bound, may form:

(7) a substituted (as defined below) or unsubstituted, saturated, unsaturated or aromatic 4-, 5- or 6- membered ring that contains carbon atoms, the nitrogen atom of the Amide group (2)) and optionally one further heteroatom chosen from oxygen, sulfur and nitrogen, and preferably nitrogen (hereinbelow also referred to as "Ring (7)").

Ring (7) is preferably a 5- or 6-membered ring and most preferably a 5-membered ring.

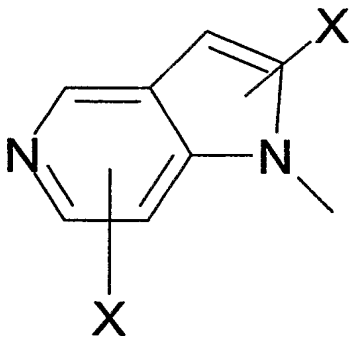
Ring (7) preferably comprises carbon atoms, the nitrogen atom of the Amide group (2) and optionally one further nitrogen atom in the group R_a that forms the bridge between the nitrogen atom of the Amide group (2) and the Ring (1), in which said nitrogen atom is preferably separated from the nitrogen atom of the amide bond by 2 or preferably 1 carbon atoms, for example as shown the formulas below.

Ring (7) may be saturated, unsaturated and/or aromatic. When Ring (7) is a 5- or 6-membered ring, it preferably contains a double bond in the group R_a that forms the bridge between the nitrogen atom of the Amide group (2) and the Ring (1). More preferably, said double bond is present on the carbon atom or the nitrogen atom of the bridge R_a that is bound to the Ring (1), for example as shown in the Formulas below.

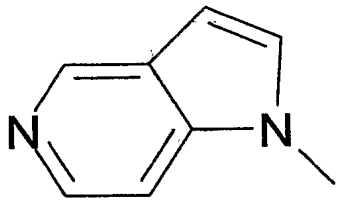
Ring (7) may be unsubstituted or may be substitited on the group R_a that forms the bridge between the nitrogen atom of the Amide group (2) and the Ring (1), i.e. with one or more substituent that are independently and suitably chosen from halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, cyano, nitro, hydroxy and an amino group NR_dR_e (in which R_d and R_e are as defined herein).

Some specific, but non-limiting examples of groups that may be present as the fused bicyclic nucleus formed by Ring (1) and Ring (7) are:

a) a group

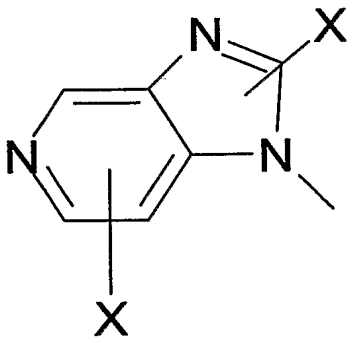


which represents a 5-azaindole group

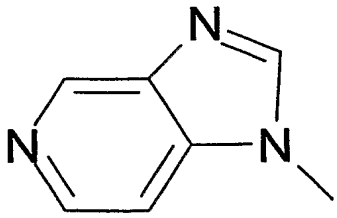


that is unsubstituted (X=H) or that be may be substituted, i.e. independently on any one of the rings or on both rings, with 1 or 2 substituents X, in which said 1 or 2 substituents X are independently and suitably chosen from the substituents X as mentioned for Ring (1) and for Ring (7), respectively, hereinabove;

b) a group



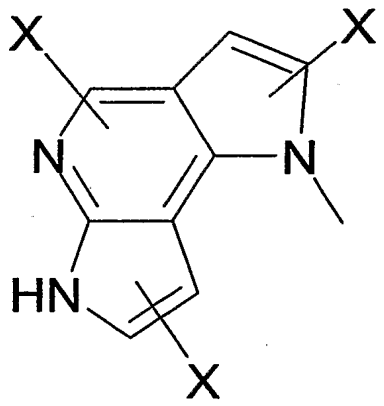
which represents a 1*H*-imidazo[4,5-*c*} pyridine (or "5-azabenzimidazole) group



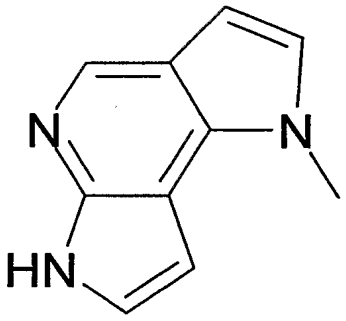
that is unsubstituted (X=H) or that be may be substituted, i.e. independently on any one of the rings or on both rings, with 1 or 2 substituents X (and in the case of Ring (7) with only one such substituent X), in which said 1 or 2 substituents X are independently and suitably chosen from the substituents X as mentioned for Ring (1) and for Ring (7), respectively, hereinabove.

The compounds of the invention may also contain both a Ring (6) and a Ring (7), that together with Ring (1) form a tricyclic ring system, in which Ring (1), Ring (6) and Ring (7) are as described herein. Some preferred, but non-limiting examples of a tricyclic ring system comprising Ring (1), a Ring (6) and a Ring (7) are:

a) a group

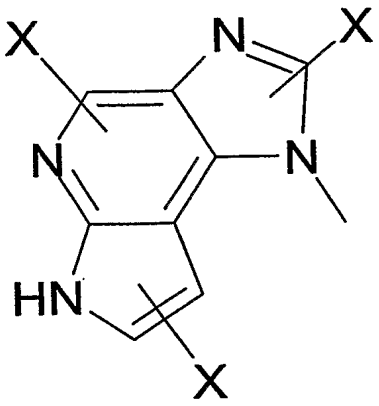


which represents a 1,6-dihydro-1,5,6-triaza-*as*-indacene group

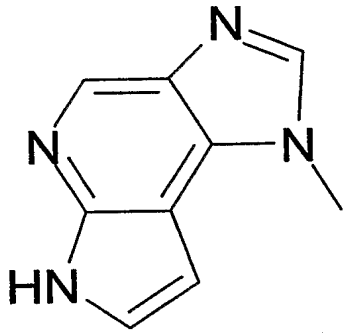


that is unsubstituted (X=H) or that be may be substituted, i.e. independently on any one of the rings, any two of the rings or on all three of the rings, with 1 or 2 substituents X (and in the case of Ring (1) with only one such substituent X), in which said 1 or 2 substituents X are independently and suitably chosen from the substituents X as mentioned for Ring (1), Ring (6) and Ring (7), respectively, hereinabove.

b) a group



which represents a 1,6-dihydro-1,3,5,6-tetra-aza-*as*-indacene group



that is unsubstituted (X=H) or that be may be substituted, i.e. independently on any one of the rings, any two of the rings or on all three of the rings, with 1 or 2 substituents X (and in the case of Ring (1) and Ring (7) with only one such substituent X), in which said 1 or 2 substituents X are independently and suitably chosen from the substituents X as mentioned for Ring (1), Ring (6) and Ring (7), respectively, hereinabove.

Thus, in one embodiment, the compounds of the invention contain a bicylic nucleus comprised of Ring (1) and a Ring (6), in which said Ring (1) and Ring (6) are as further defined herein. In such a bicyclic nucleus, either of Ring (1) and Ring (6) may be aromatic, or Rings (1) and (6) may together form an aromatic bicyclic nucleus.

In another embodiment, the compounds of the invention contain a bicylic nucleus comprised of Ring (1) and a Ring (7), in which said Ring (1) and Ring (7) are as further defined herein. In such a bicyclic nucleus, either of Ring (1) and Ring (7) may be aromatic, or Rings (1) and (7) may together form an aromatic bicyclic nucleus.

In yet another embodiment, the compounds of the invention contain a tricyclic nucleus comprised of Ring (1), a Ring (6) and a Ring (7), in which said Ring (1), said Ring (6) and said Ring (7) are as further defined herein. In such a bicyclic nucleus, each of Ring (1), Ring (6) and Ring (7) may be aromatic, or Rings (1) and (6) may together form an aromatic bicyclic nucleus, or Rings (1) and (7) may together form an aromatic bicyclic nucleus, or Rings (1), (6) and (7) may together from an aromatic tricyclic nucleus.

Preferably, the compounds of the invention contain only a Ring (1), or a Ring (1) and a Ring (6), but no Ring (7).

In the compounds of the invention, Ring (3) is preferably is a 5- or 6-membered ring containing carbon atoms and optionally 1 or 2, and preferably 1, hetero-atoms chosen from nitrogen, oxygen and sulfur. More preferably, Ring (3) is a 5- or 6-membered ring containing only carbon atoms.

In the compounds of the invention, Ring (3) is may be saturated, contain 1 or 2 unsaturated bonds, or may be aromatic, with saturated and aromatic rings being particularly preferred.

As indicated above, in the compounds of the invention, the Ring (3) is connected to the carbon atom of the Amide group (2), and also carries the Alkylene amino group (4). When the Ring (3) is a 5-membered ring, the Alkylene amino group (5) is preferably in the 3- position or the 4-position relative to the carbon atom of Ring (3) that is bound to the carbon atom of the Amide group (2). When the Ring (3) is a 6-membered ring, the Alkylene amino group (4) is preferably in the 3-, 4- or 5- position relative to the carbon atom of Ring (3) that is bound to the carbon atom of the Amide group (2), and most preferably in the 4-position. However, as will be clear from the above, the invention generally comprises all isomers with respect to the positions of the Amide group (2) and the Alkylene aminogroup (4) on the Ring (3), as long as in the final molecule according to Formula I, the distance between the at least one hydrogen-accepting hetero atom in

Ring (1) and the nitrogen atom of the amino group in the Alkylene aminogroup (4) is in the range indicated above.

It will be clear to the skilled person that when Ring (3) is a saturated ring, said ring may be in the form of different stereoisomers with respect to the way the Amide group (2) and the Alkylene aminogroup (4) are bound to said Ring (3), i.e. as *cis*- and *trans*- isomers. Both are included within the scope of the invention, with the *trans*-isomer being particularly preferred.

It will also be clear to the skilled person that when Ring (3) is a saturated ring that contains one or more substituents, Ring (3) may contain one or more chiral carbon atoms and may thus exist as different isomers, e.g. enantiomers or diastereomers. All such isomers are included within the scope of the invention.

In the compounds of the invention, Ring (3) is may be unsubstituted or substituted with 1-4, preferably 1 or 2, substituents independently and suitably chosen from halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, substituted or unsubstituted aryl, cyano, nitro, hydroxy and an amino group NR_dR_e (in which R_d and R_e are as defined herein). These possible substituents on Ring (6) are also generally indicated in the formula's below with "Y", it being understood that, in accordance with the foregoing, 0, or 1-4, and preferably 0, 1 or 2, such substituents may be present, in which each time such a substituent is present, it may be independently and suitably chosen from the group mentioned above, and it may be present on any suitable position of the ring.

Some specific, but non-limiting examples of groups that may be present as the Ring (3) are cyclopentylene, cyclopentenylene, cyclohexylene, cyclohexenylene, cyclohexdienylene and phenylene, which are connected to the Amide group (2) and the Alkylene amino group (4) as indicated above and which may be unsubstituted or substituted with 1 or 2 substituents independently and suitably chosen from halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, substituted or unsubstituted aryl, cyano, nitro, hydroxy and an amino group NR_dR_e (in which R_d and R_e are as defined herein).

Accordingly, some examples of Ring (3) include, but are not limited to, 1,3-cyclopentylene; 1,4-cyclopent-2-enylene; 1,3- and in particular 1,4-cyclohexylene; 1,3-1,4- or 1,5-cyclohex-2-enylene; 1,3-, 1,4- or 1,5-cyclohex-3-enylene; 1,3-, 1,5- and in particular 1,4-cyclohex-2,5-dienylene, and 1,3- and in particular 1,4-phenylene; of which

3-cyclopentylene; 1,3- and 1,4-cyclohexylene; and 1,3- and 1,4-phenylene are preferred, and 1,4-cyclohexylene and 1,4 phenylene are most preferred (and in which the numbers refer to the positions on which the Amide group (2) and the Alkylene aminogroup (4) are bound to Ring (3), respectively).

In the compounds of the invention, n in the Alkylene aminogroup (4) may be 0, so that the Alkylene aminogroup (4) is in fact not an alkylene aminogroup but an aminogroup-NR_bR_c; or may be 2, so as to form an ethyleneaminogroup of the formula $-(CR_1R_2\text{-}CR_1R_2)\text{-}NR_bR_c$; as long as (in both cases) in the final molecule according to Formula I, the distance between the at least one hydrogen-accepting hetero atom in Ring (1) and the nitrogen atom of the amino group in the Alkylene aminogroup (4) is in the range indicated above.

However, n is preferably 1, so as to form a methyleneamino group of the formula $-CR_1R_2\text{-}NR_bR_c$.

In the alkylene amino group (4), each time a group R_1 or R_2 is present, said group may be the same or different and may be independently and suitably chosen from the group consisting of: halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, substituted or unsubstituted aryl, cyano, hydroxy; with hydrogen, substituted or unsubstituted C_1-C_6 alkyl and substituted or unsubstituted aryl being preferred. In particular, each R_1 and R_2 are independently and suitably chosen from the group consisting of hydrogen, methyl or ethyl. For example, when one of R_1 and R_2 is hydrogen, the other may may be a methyl or ethyl.

It will be clear to the skilled person that when R_1 and R_2 are different, the compounds of the invention may exist as different isomers, e.g. enantiomers or diastereomers. All such isomers are included within the scope of the invention.

The amino group -NR_bR_c is such that, at a pH in the range of 5.0 – 9.0 , preferably 6.0 – 8.0 , such as pH about 7.0, it is essentially in a protonated form. "*Essentially in a protonated form*" is herein generally means that at least 50%, preferably at least 75%, more preferably at least 90%, even more preferably at least 95% of all amino groups are protonated at the pertinent pH. Whether or not an amino group -NR_bR_c is essentially in a protonated form at a pH in the range above may be calculated using a suitable computer algorithm or may be determined experimentally using a technique known per se for determining the pK_a.

In the compounds of the invention, R_b and R_c may be the same or different and are preferably independently and suitably chosen from the group consisting of hydrogen, substituted or unsubstituted C_1-C_{10}, and preferably C_1-C_6, alkyl.

Accordingly, some particular, but non-limiting examples of the group $-NR_bR_c$ are: amino, methylamino, ethylamino, n-propylamino, i-propylamino, n-butylamino, i-butylamino, t-butylamino, dimethylamino, ethylmethylamino, methyl-n-propylamino, methyl-i-propylamino, n-butylmethylamino, i-butylmethylamino, t-butylmethylamino, diethylamino, ethyl-n-propylamino, ethyl-i-propylamino, n-butylethylamino, i-butylethylamino, t-butylethylamino, di-n-propylamino, di-i-propylamino, di-n-butylamino, di-i-propylamino, di-t-butylamino, as well as mono- or dialkylamino groups in which one or both of the alkyl groups contain more than 4 carbon atoms, such as the various isomers of pentylamino, hexylamino, heptylamino, octylamino, nonylamino, decylamino, dipentylamino, dihexylamino, diheptylamino, dioctylamino, dinonylamino, didecylamino methylpentylamino, methylhexylamino, methylheptylamino, methyloctylamino, methylnonylamino, methyldecylamino, ethylpentylamino, ethylhexylamino, ethylheptylamino, ethyloctylamino, ethylnonylamino, ethyldecylamino, propylpentylamino, propylhexylamino, propylheptylamino, propyloctylamino, propylnonylamino, propyldecylamino.

The above groups may be substituted or unsubstituted, but when they are substituted, they are preferably not substituted on a carbon atom that is attached to the nitrogen atom of the amino group $-NR_bR_c$.

Preferably, in the compounds of the invention, R_b and R_c may be the same or different and are preferably chosen from hydrogen and C_1-C_6 alkyl, more preferably C_1-C_4 alkyl, such as C_1, C_2 and/or C_3 alkyl, such as methyl, ethyl, i-propyl and n-propyl.

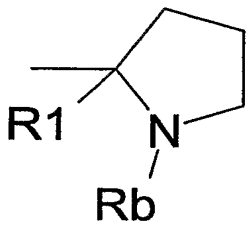
Alternatively, and although less preferred, R_b, R_c and the nitrogen atoms to which they are bound may together from a ring with between 3 and 10, preferably between 4 and 7, and most preferably 5 or 6 atoms in the ring (including the nitrogen atom to which both R_a and R_b are bound). This ring consists of one nitrogen atom, carbon atoms and optionally one further hetero-atom chosen from oxygen, nitrogen and sulfur, but preferably contains only carbon atoms and 1 or 2 nitrogen atoms, most preferably only carbon atoms and only one nitrogen atom. Said ring may optionally also be substituted

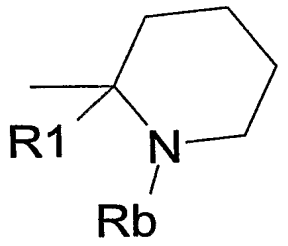
(as defined above), and may in particular be substituted with one or more, and in particular one or two, C_1-C_6 alkyl groups; and said ring may contain a double bond and/or be aromatic (although aromatic rings may be less preferred, as they may not be easily protonated at a pH in the ranges mentioned above. For the same reason, although an amino group $-NR_bR_c$ in which R_b and/or R_c is a substituted or unsubstituted aryl is not excluded, such amino groups are again less preferred).

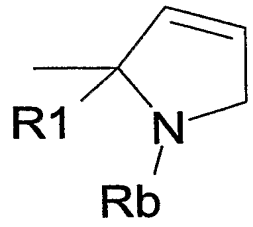
Some specific, but non-limiting examples of such non-aromatic cyclic groups $-NR_aR_b$ are pyrrolidinyl, piperazinyl, morpholinyl and piperidinyl, all of which may be unsubstituted and may optionally also be substituted (as defined above), and may in particular be substituted with with one or more, and in particular one or two, C_1-C_6 alkyl groups.

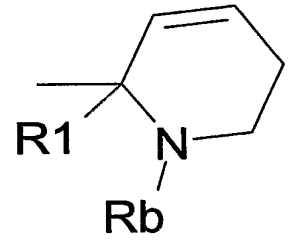
In the invention, R_d and R_e may each independently be one of the groups mentioned for R_b and R_c above (including the structures in which N, R_b and R_c together form a ring), but may also each independently be substituted or unsubstituted aryl (In this respect, it should be noted that the requirement mentioned above for the amino group - NR_bR_c - i.e. that it is in essentially protonated form at a pH in the range of 5.0 and 9.0 - may, but does not necessarily need to apply to the amino group $-NR_dR_e$).

Also, in the invention, one of R_b and R_c may, together with the nitrogen atom of the amino group$-NR_bR_c$, one of R_1 and R_2 and the carbon atom to which R_1 and R_2 are bound, form a substituted or unsubstituted 5 or 6 membered ring that contains carbon atoms, the nitrogen atom of the amino group $-NR_bR_c$ and optionally one further nitrogen atom and that may be saturated or contain one double bond. Some preferred, but non-limiting examples of such groups (in which the ring is formed by R_2 and R_c) are:









which may be substituted or unsubstituted as indicated above and in which R_1 and R_b are as indicated above.

In the compounds of the invention, the Ring (1), Ring (3) and the Alkylene aminogroup (4) are preferably chosen such, and connected to each other in such a way, that the distance between the at least one hydrogen-accepting hetero atom in Ring (1) and the nitrogen atom of the amino group in the Alkylene amino group (4), as determined using a Scatter Plot (generated as indicated above), is in the range of 11.0 to 11.8, preferably from 11.0 to 11.6, more preferably from 11.0 to 11.4 Angstrom.

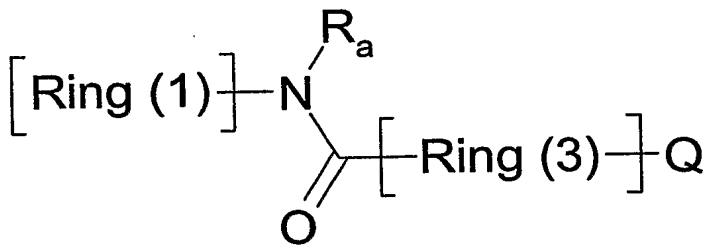
The distance between the at least one hydrogen-accepting hetero atom in Ring (1) and the nitrogen atom of the amino group in the Alkylene amino group can be determined using a commercially available computer algorithm, such as the software package MOE (Chemical Computing Group, Inc, Quebec, Canada), version 2003.02, on SGI Fuel hardware, running IRIX 6.5. Generally, the default parameters for the software can be used, unless indicated differently. In particular, this N-N distance can be calculated according to the following procedure:

- The molecules are drawn using the molecule builder of MOE 2003.02. The primary amine function is protonated by forcing a positive charge on the nitrogen. Where possible, the amide function is put in a CIS position to mimic the active conformation. Molecules are minimized using the MMFF94 force field as implemented in MOE 2003.02. The default minimization parameters and procedures of MOE 2003.02 are applied.
- A stochastic conformational search is applied on the minimized structure. The default parameters are applied with the exception of the option to rotate around amide and double bonds. Furthermore, the energy cutoff parameter is set to 5 kcal/mol.
- The N-N distance of the energetically lowest conformation is measured using the standard procedures available in MOE 2003.02. These distances can also be represented schematically as a Scatter Plot, as shown in the Figure.

According to one particularly preferred, but non-limiting embodiment, in order to achieve such a distance between the at least one hydrogen-accepting hetero atom in Ring (1) and the nitrogen atom of the amino group in the Alkylene amino group (4), Ring (1) is a saturated, unsaturated and/or aromatic six membered ring with the at least one hydrogen-accepting hetero atom in the 4-position relative to the Amide group (2), that may be fused with one or two other rings as mentioned above (i.e. Ring (6) and/or (7)); Ring (3) is a saturated, unsaturated and/or aromatic six membered ring in which the Alkylene aminogroup (4) is in the 4-position relative to the Amide group (2); and the Alkylene aminogroup (4) is a methyleneamino group $-CR_1R_2-NR_bR_c$ (i.e. with n being 1 and R_1, R_2, R_b and R_c being as defined hereinabove).

However, generally, any combination of groups that is chosen for Ring (1), Ring (3) and the alkylene aminogroup (4) within the definitions mentioned above so as to achieve such a distance between the at least one hydrogen-accepting hetero atom in Ring (1) and the nitrogen atom of the amino group in the Alkylene amino group (4) can be used in the invention.

Thus, generally, the invention relates to compounds of Formula I,



(I)

in which:

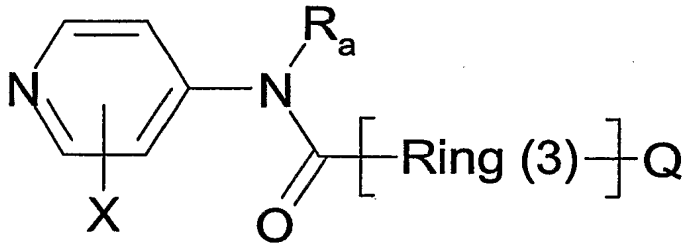
- Ring (1) is a substituted or unsubstituted, saturated, unsaturated or aromatic 4-, 5-, 6-, 7- or 8-membered ring containing carbon atoms and at least one hydrogen-accepting hetero-atom and optionally 1 or 2 further hetero-atoms;
- R_a is as defined above;
- Ring (3) is a substituted (as defined herein) or unsubstituted, saturated, unsaturated or aromatic 4-, 5-, 6-, 7- or 8-membered ring containing carbon atoms optionally 1 or 2 hetero-atoms;
- Q represents an alkylene aminogroup of the formula $-(CR_1R_2)_n-NR_bR_c$, in which R_1, R_2, n, R_b and R_c are as defined above and in which the amino group is such that, at a pH of between 5.0 and 9.0, preferably between 6.0 and 8.0, such as about 7.0, it is essentially in a protonated form (as defined herein);

and in which

- the distance between the at least one hydrogen-accepting hetero atom in Ring (1) and the nitrogen atom of the amino group in the group Q, as determined using a Scatter Plot (generated as indicated above), is in the range of 11.0 to 11.8, preferably 11.0 to 11.6, and more preferably 11.0 to 11.4 Angstrom.

Preferred definitions for Ring (1), R_a, Ring (3) and the substituents X are as mentioned above; and n and the groups R_1, R_2, R_a and R_b in the group Q are preferably in accordance with the preferences mentioned above for the Alkylene aminogroup (4).

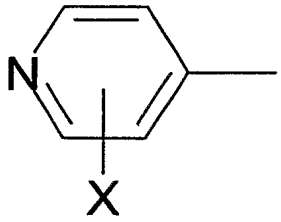
According to one preferred, but non-limiting embodiment, the invention relates to a compound of the formula (II):



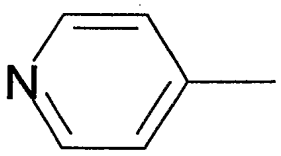
(II)

in which:

- the group



represents a 4-pyridinyl group



that may be unsubstituted (i.e. X = hydrogen) or that may be substituted with 1-4, preferably 1 or 2, substituents X that are each time independently and suitably chosen from halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, substituted or unsubstituted aryl, nitro, hydroxy and an amino group NR_dR_e (in which R_d and R_e are as defined herein);

- R_a, Ring (3) and Q are as defined above;

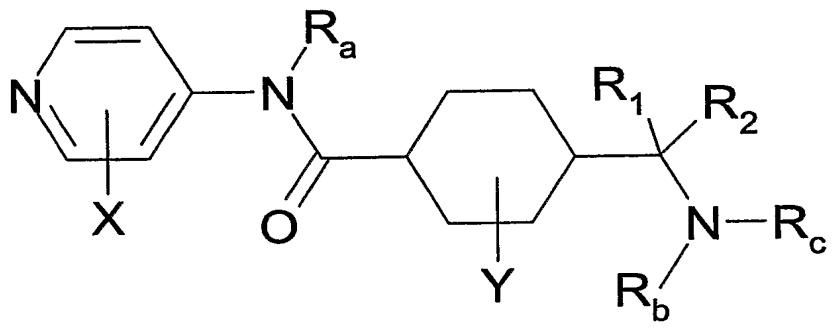
and in which:

- the distance between the nitrogen atom in the 4-pyridylgroup and the nitrogen atom of the amino group in the group Q, as determined using a Scatter Plot

(generated as indicated above), is in the range of 11.0 to 11.8, preferably 11.0 to 11.6, and more preferably 11.0 to 11.4 Angstrom.

Preferred definitions for R_a, Ring (3) and the substituents X are as mentioned above; and n and the groups R_1, R_2, R_b and R_c in the group Q are preferably in accordance with the preferences mentioned above for the Alkylene aminogroup (4).

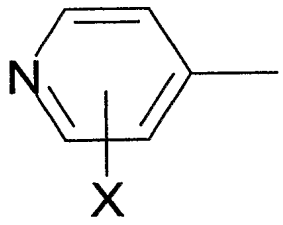
According to one particularly preferred, but non-limiting, aspect of this preferred embodiment, the invention relates to a compound of the formula (III):



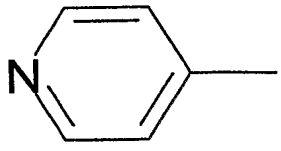
(III)

in which:

- the group

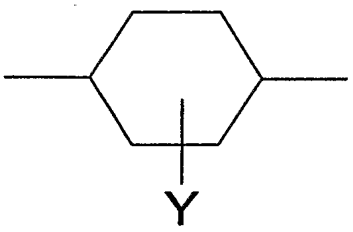


represents a 4-pyridinyl group

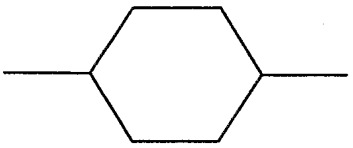


that may be unsubstituted (i.e. X = hydrogen) or that may be substituted with 1-4, preferably 1 or 2, substituents X that are each time independently and suitably chosen from from halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, substituted or unsubstituted aryl, nitro, hydroxy and an amino group NR_dR_e (in which R_d and R_e are as defined herein);

- the group



represents a 1,4-cyclohexylene group

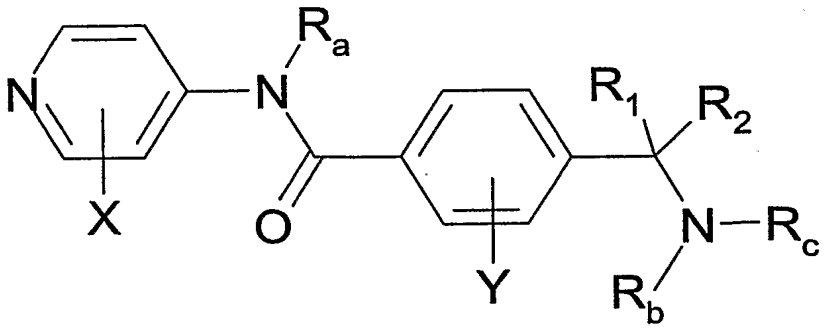


that may be unsubstituted (i.e. Y = hydrogen) or that may be substituted with 1-4, preferably 1 or 2, substituents Y that are each time independently and suitably chosen from halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, substituted or unsubstituted aryl, nitro, hydroxy and an amino group NR_dR_e (in which R_d and R_e are as defined herein);

- R_a, R_1, R_2, R_b and R_c are as defined above.

Preferred definitions for R_a, the substituents X, the substituents Y, the groups R_1, R_2, R_a and R_b and n are as mentioned above.

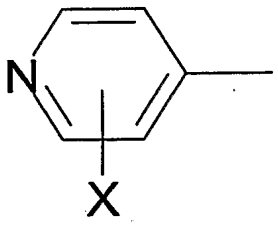
According to another particularly preferred, but non-limiting, aspect of this preferred embodiment, the invention relates to a compound of the formula (IV):



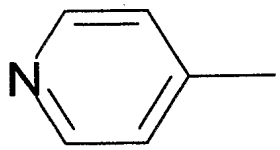
(IV)

in which:

- the group

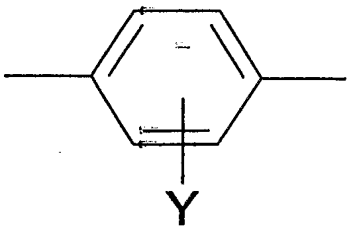


represents a 4-pyridinyl group

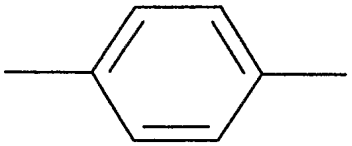


that may be unsubstituted (i.e. X = hydrogen) or that may be substituted with 1-4, preferably 1 or 2, substituents X that are each time independently and suitably chosen from halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, substituted or unsubstituted aryl, nitro, hydroxy and an amino group NR_dR_e (in which R_d and R_e are as defined herein);

- the group



represents a 1,4-phenylene group

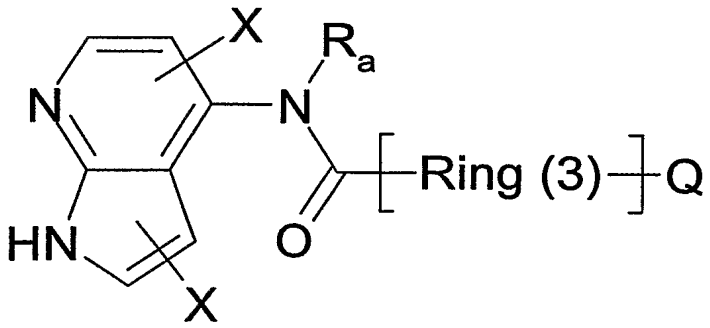


that may be unsubstituted (i.e. Y = hydrogen) or that may be substituted with 1-4, preferably 1 or 2, substituents Y that are each time independently and suitably chosen from halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, substituted or unsubstituted aryl, nitro, hydroxy and an amino group NR_dR_e (in which R_d and R_e are as defined herein);

- R_a, R_1, R_2, R_b and R_c are as defined above.

Preferred definitions for R_a, the substituents X, the substituents Y, the groups R_1, R_2, R_a and R_b and n are as mentioned above.

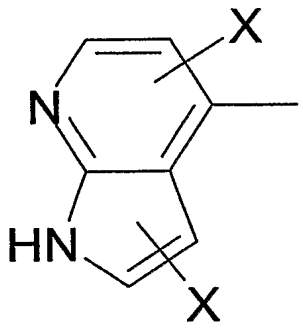
According to another preferred, but non-limiting embodiment, the invention relates to a compound of the formula (V):



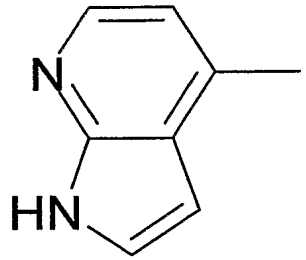
(V)

in which:

- the group



represents a 7-azaindole group

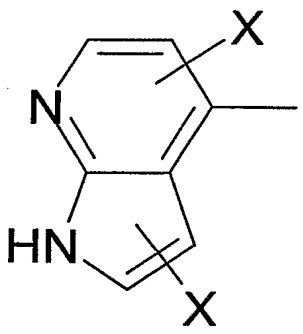


in which each ring may be unsubstituted (i.e. X = hydrogen) or in which each ring or both rings may independently be substituted with 1 or 2 substituents X that are each time independently and suitably chosen from halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, substituted or unsubstituted aryl, nitro, hydroxy and an amino group NR_dR_e (in which R_d and R_e are as defined herein);

- R_a, Ring (3) and Q are as defined above;

and in which:

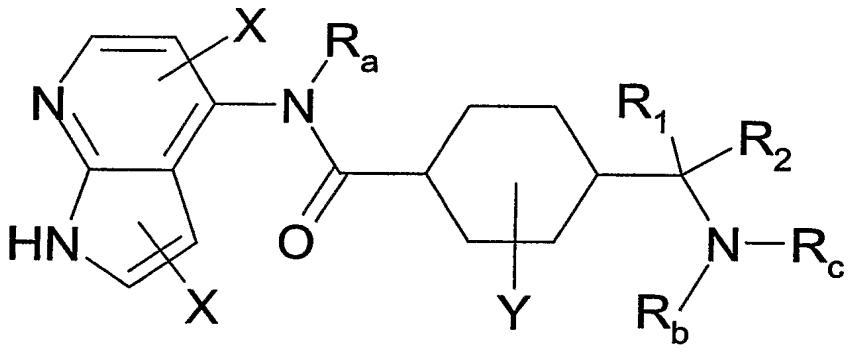
- the distance between the pyridine-nitrogen atom in the group



and the nitrogen atom of the amino group in the group Q, as determined using a Scatter Plot (generated as indicated above), is in the range of 11.0 to 11.8, preferably 11.0 to 11.6, and more preferably 11.0 to 11.4 Angstrom.

Preferred definitions for R_a, Ring (3) and the substituents X are as mentioned above; and n and the groups R_1, R_2, R_b and R_c in the group Q are preferably in accordance with the preferences mentioned above for the Alkylene aminogroup (4).

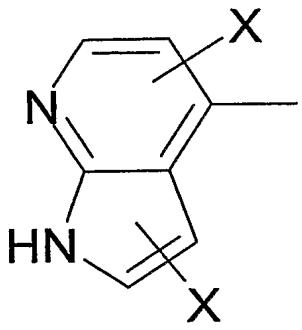
According to one particularly preferred, but non-limiting, aspect of this preferred embodiment, the invention relates to a compound of the formula (VI):



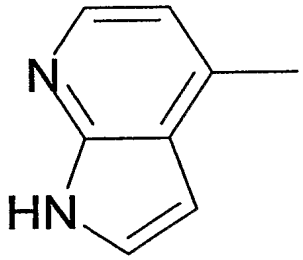
(VI)

in which:

- the group

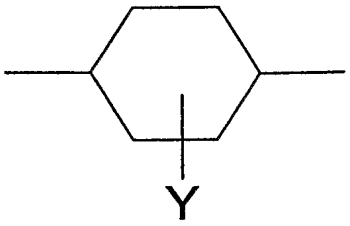


represents a 7-azaindole group

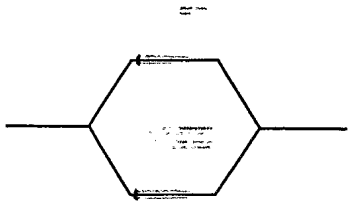


in which each ring may be unsubstituted (i.e. X = hydrogen) or in which each ring or both rings may independently be substituted with 1 or 2 substituents X that are each time independently and suitably chosen from halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, substituted or unsubstituted aryl, nitro, hydroxy and an amino group NR_dR_e (in which R_d and R_e are as defined herein);

- the group



represents a 1,4-cyclohexylene group

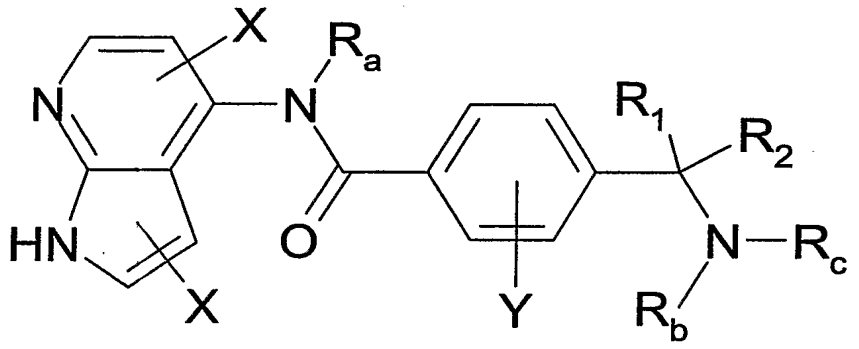


that may be unsubstituted (i.e. Y = hydrogen) or that may be substituted with 1-4, preferably 1 or 2, substituents Y that are each time independently and suitably chosen from halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, substituted or unsubstituted aryl, nitro, hydroxy and an amino group NR_dR_e (in which R_d and R_e are as defined herein);

- R_a, R_1, R_2, R_b and R_c are as defined above.

Preferred definitions for R_a, the substituents X, the substituents Y, the groups R_1, R_2, R_b and R_b and n are as mentioned above.

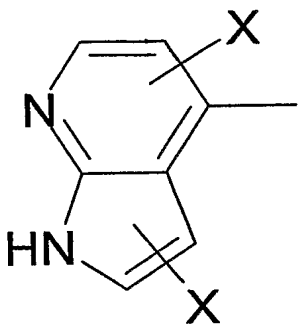
According to another particularly preferred, but non-limiting, aspect of this preferred embodiment, the invention relates to a compound of the formula (VI):



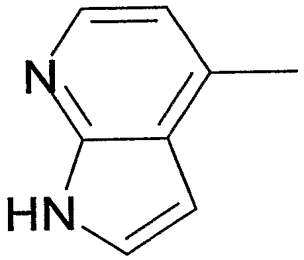
(VII)

in which:

- the group

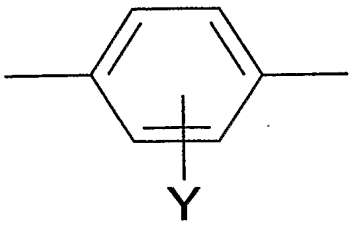


represents a 7-azaindole group

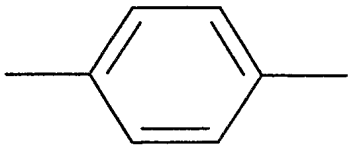


in which each ring may be unsubstituted (i.e. X = hydrogen) or in which each ring or both rings may independently be substituted with 1 or 2 substituents X that are each time independently and suitably chosen from halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, substituted or unsubstituted aryl, nitro, hydroxy and an amino group NR_dR_e (in which R_d and R_e are as defined herein);

the group



represents a 1,4-phenylene group

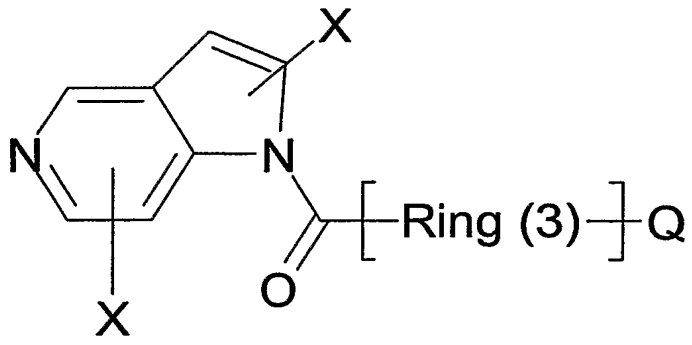


that may be unsubstituted (i.e. Y = hydrogen) or that may be substituted with 1-4, preferably 1 or 2, substituents Y that are each time independently and suitably chosen from halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, substituted or unsubstituted aryl, nitro, hydroxy and an amino group NR_dR_e (in which R_d and R_e are as defined herein);

- R_a, R_1, R_2, R_b and R_c are as defined above.

Preferred definitions for R_a, the substituents X, the substituents Y, the groups R_1, R_2, R_b and R_c and n are as mentioned above.

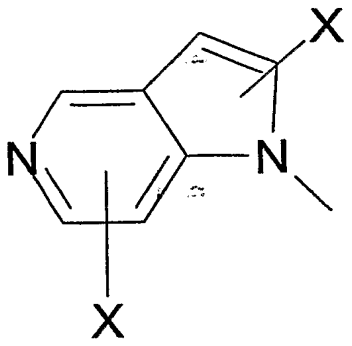
According to another preferred, but non-limiting embodiment, the invention relates to a compound of the formula (VI):



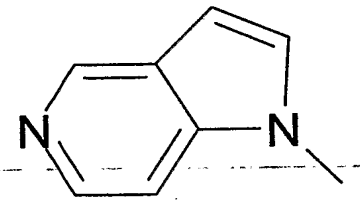
(VIII)

in which:

- the group



represents a 5-azaindole group

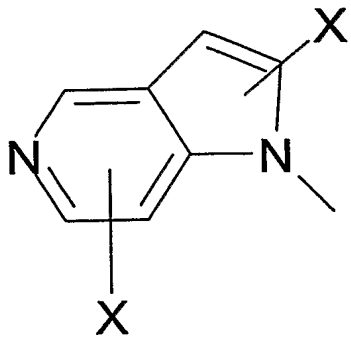


in which each ring may be unsubstituted (i.e. X = hydrogen) or in which each ring or both rings may independently be substituted with 1 or 2 substituents X that are each time independently and suitably chosen from halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, substituted or unsubstituted aryl, nitro, hydroxy and an amino group NR_dR_e (in which R_d and R_e are as defined herein);

- Ring (3) and Q are as defined above;

and in which:

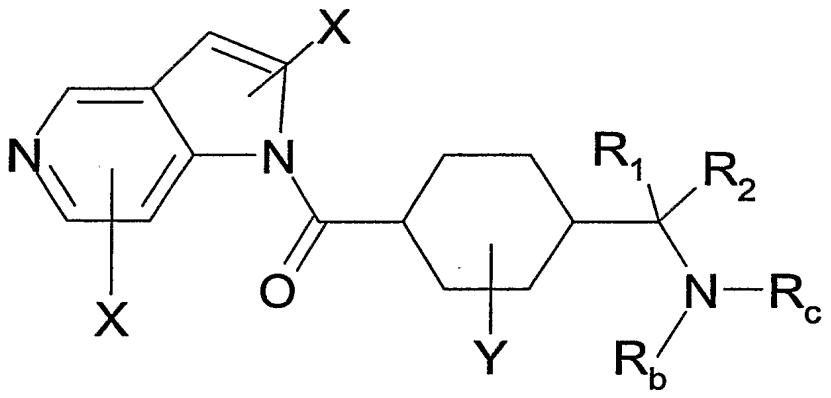
- the distance between the pyridine-nitrogen atom in the group



and the nitrogen atom of the amino group in the group Q, as determined using a Scatter Plot (generated as indicated above), is in the range of 11.0 to 11.8, preferably 11.0 to 11.6, and more preferably 11.0 to 11.4 Angstrom.

Preferred definitions for Ring (3) and the substituents X are as mentioned above; and n and the groups R_1, R_2, R_b and R_c in the group Q are preferably in accordance with the preferences mentioned above for the Alkylene aminogroup (4).

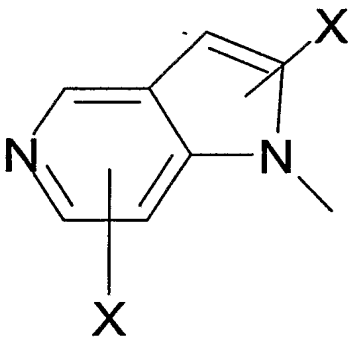
According to one particularly preferred, but non-limiting, aspect of this preferred embodiment, the invention relates to a compound of the formula (IX):



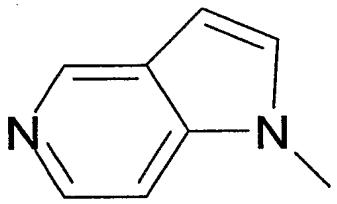
(IX)

in which:

- the group

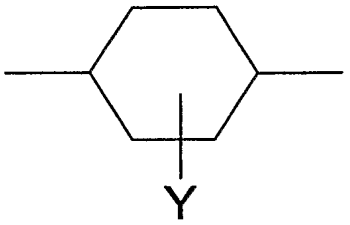


represents a 5-azaindole group

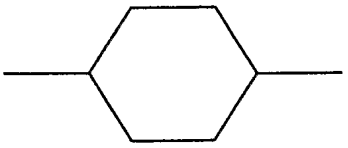


in which each ring may be unsubstituted (i.e. X = hydrogen) or in which each ring or both rings may independently be substituted with 1 or 2 substituents X that are each time independently and suitably chosen from halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, substituted or unsubstituted aryl, nitro, hydroxy and an amino group NR_dR_e (in which R_d and R_e are as defined herein);

the group



represents a 1,4-cyclohexylene group

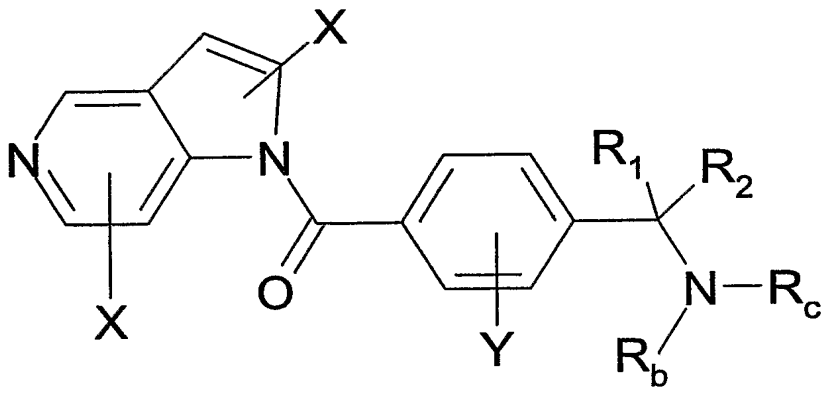


that may be unsubstituted (i.e. Y = hydrogen) or that may be substituted with 1-4, preferably 1 or 2, substituents Y that are each time independently and suitably chosen from halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, substituted or unsubstituted aryl, nitro, hydroxy and an amino group NR_dR_e (in which R_d and R_e are as defined herein);

- R_1, R_2, R_b and R_c are as defined above.

Preferred definitions for the substituents X, the substituents Y, the groups R_1, R_2, R_b and R_c and n are as mentioned above.

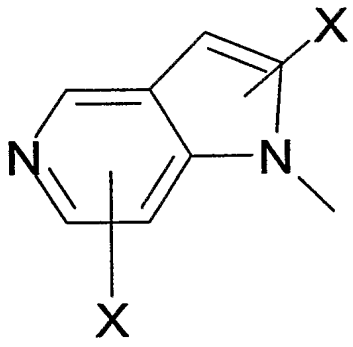
According to another particularly preferred, but non-limiting, aspect of this preferred embodiment, the invention relates to a compound of the formula (X):



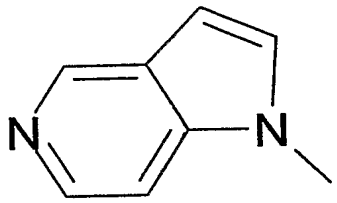
(X)

in which:

- the group

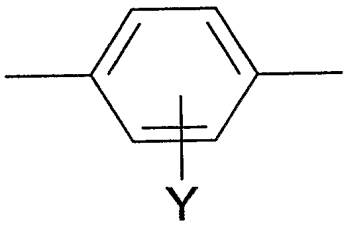


represents a 5-azaindole group

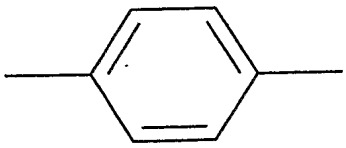


in which each ring may be unsubstituted (i.e. X = hydrogen) or in which each ring or both rings may independently be substituted with 1 or 2 substituents X that are each time independently and suitably chosen from halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, substituted or unsubstituted aryl, nitro, hydroxy and an amino group NR_dR_e (in which R_d and R_e are as defined herein);

- the group



represents a 1,4-phenylene group

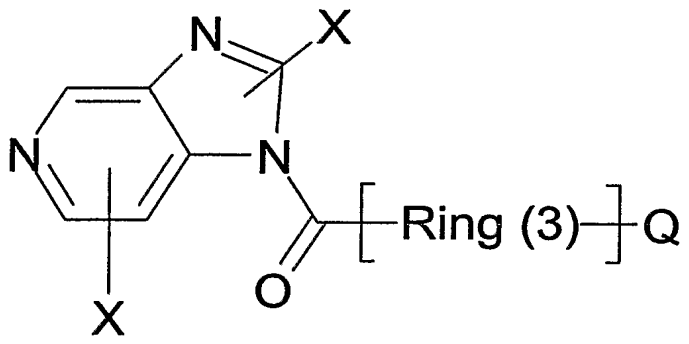


that may be unsubstituted (i.e. Y = hydrogen) or that may be substituted with 1-4, preferably 1 or 2, substituents Y that are each time independently and suitably chosen from halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, substituted or unsubstituted aryl, nitro, hydroxy and an amino group NR_dR_e (in which R_d and R_e are as defined herein);

- R_1, R_2, R_b and R_c are as defined above.

Preferred definitions for the substituents X, the substituents Y, the groups R_1, R_2, R_b and R_c and n are as mentioned above.

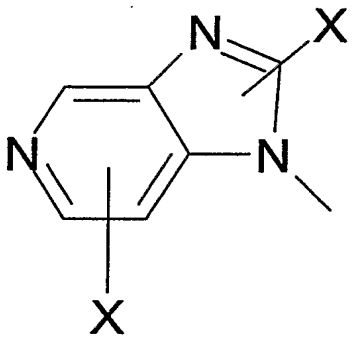
According to another preferred, but non-limiting embodiment, the invention relates to a compound of the formula (XI):



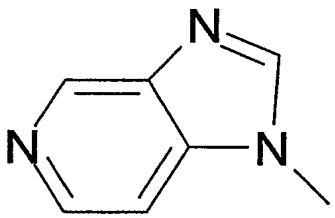
(XI)

in which:

- the group



represents a group

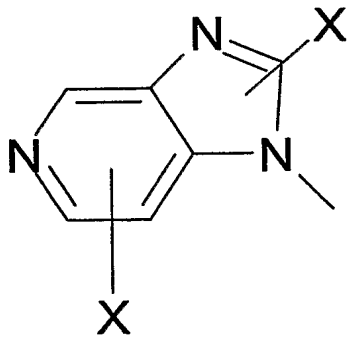


in which each ring may be unsubstituted (i.e. X = hydrogen) or in which each ring or both rings may independently be substituted with 1 or 2 substituents X (and in the case of Ring (7) with only one such substituent X) that are each time independently and suitably chosen from halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, substituted or unsubstituted aryl, nitro, hydroxy and an amino group NR_dR_e (in which R_d and R_e are as defined herein);

Ring (3) and Q are as defined above;

and in which:

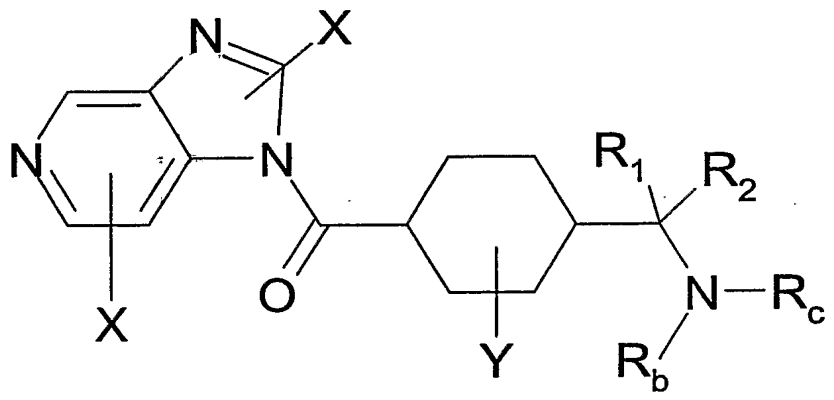
- the distance between the pyridine-nitrogen atom in the group



and the nitrogen atom of the amino group in the group Q, as determined using a Scatter Plot (generated as indicated above), is in the range of 11.0 to 11.8, preferably 11.0 to 11.6, and more preferably 11.0 to 11.4 Angstrom.

Preferred definitions for Ring (3) and the substituents X are as mentioned above; and n and the groups R_1, R_2, R_b and R_c in the group Q are preferably in accordance with the preferences mentioned above for the Alkylene aminogroup (4).

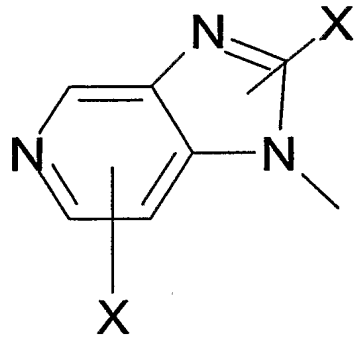
According to one particularly preferred, but non-limiting, aspect of this preferred embodiment, the invention relates to a compound of the formula (XII):



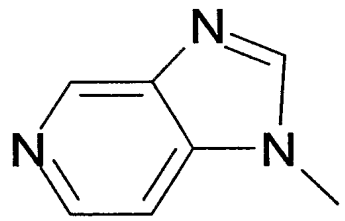
(XII)

in which:

- the group



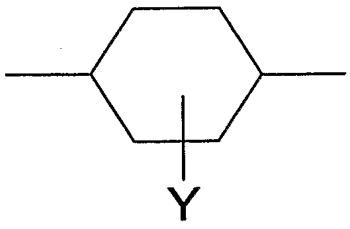
represents a group



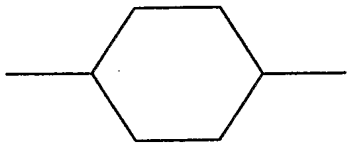
in which each ring may be unsubstituted (i.e. X = hydrogen) or in which each ring or both rings may independently be substituted with 1 or 2 substituents X (and in

case of Ring (7), with only one such substituent) that are each time independently and suitably chosen from halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, substituted or unsubstituted aryl, nitro, hydroxy and an amino group NR_dR_e (in which R_d and R_e are as defined herein);

- the group



represents a 1,4-cyclohexylene group

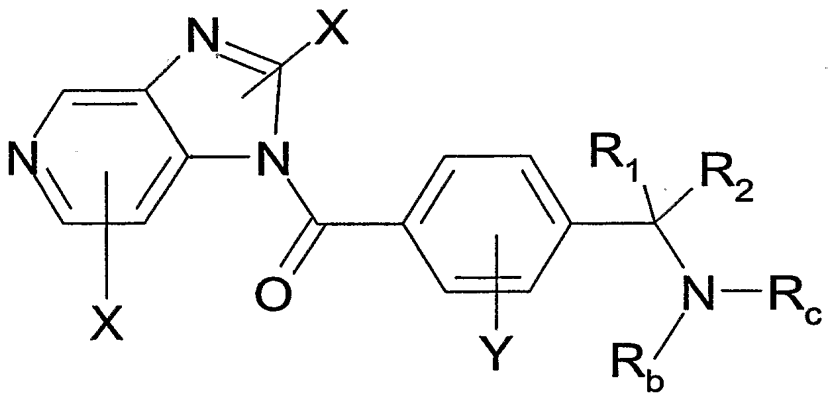


that may be unsubstituted (i.e. Y = hydrogen) or that may be substituted with 1-4, preferably 1 or 2, substituents Y that are each time independently and suitably chosen from halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, substituted or unsubstituted aryl, nitro, hydroxy and an amino group NR_dR_e (in which R_d and R_e are as defined herein);

- R_1, R_2, R_b and R_c are as defined above.

Preferred definitions for the substituents X, the substituents Y, the groups R_1, R_2, R_b and R_c and n are as mentioned above.

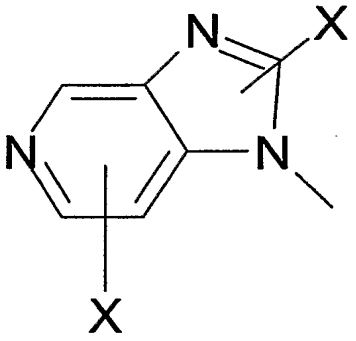
According to another particularly preferred, but non-limiting, aspect of this preferred embodiment, the invention relates to a compound of the formula (XIII):



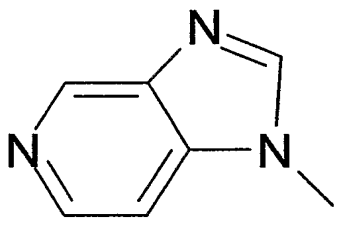
(XIII)

in which:

- the group



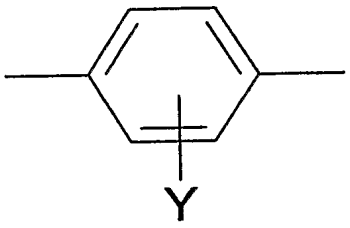
represents a group



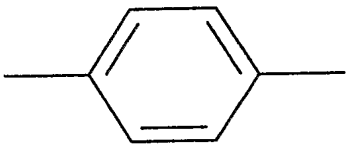
in which each ring may be unsubstituted (i.e. X = hydrogen) or in which each ring or both rings may independently be substituted with 1 or 2 substituents X (and in

the case of Ring (7) with only one such substituent X) that are each time independently and suitably chosen from halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, substituted or unsubstituted aryl, nitro, hydroxy and an amino group NR_dR_e (in which R_d and R_e are as defined herein);

- the group



represents a 1,4-phenylene group

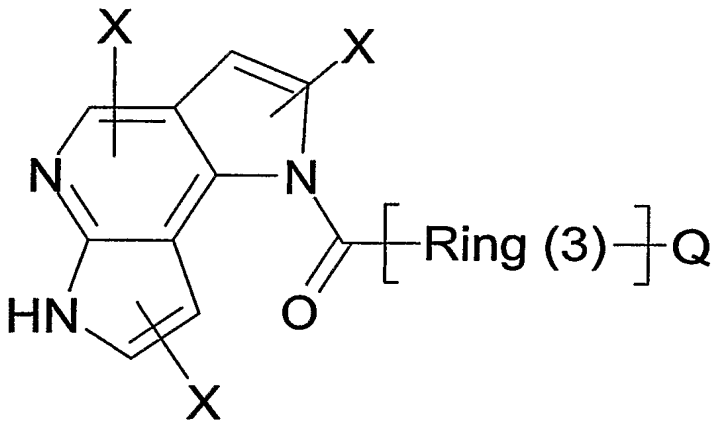


that may be unsubstituted (i.e. Y = hydrogen) or that may be substituted with 1-4, preferably 1 or 2, substituents Y that are each time independently and suitably chosen from halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, substituted or unsubstituted aryl, nitro, hydroxy and an amino group NR_dR_e (in which R_d and R_e are as defined herein);

- R_1, R_2, R_b and R_c are as defined above.

Preferred definitions for the substituents X, the substituents Y, the groups R_1, R_2, R_b and R_c and n are as mentioned above.

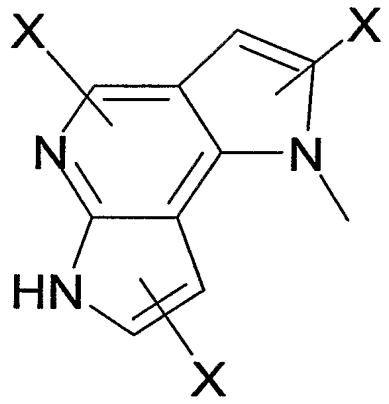
According to one particularly preferred, but non-limiting embodiment, the invention relates to a compound of the formula (XIV):



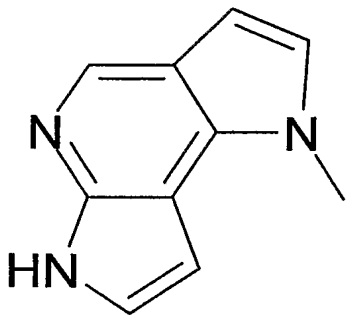
(XIV)

in which:

- the group



represents a group

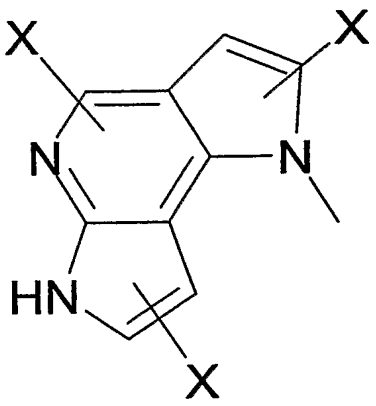


in which each ring may be unsubstituted (i.e. X = hydrogen) or in which any two of the rings or all three of the rings may independently be substituted with 1 or 2 substituents X (and in the case of Ring (1) with only one such substituent X) that are each time independently and suitably chosen from halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, substituted or unsubstituted aryl, nitro, hydroxy and an amino group NR_dR_e (in which R_d and R_e are as defined herein);

- Ring (3) and Q are as defined above;

and in which:

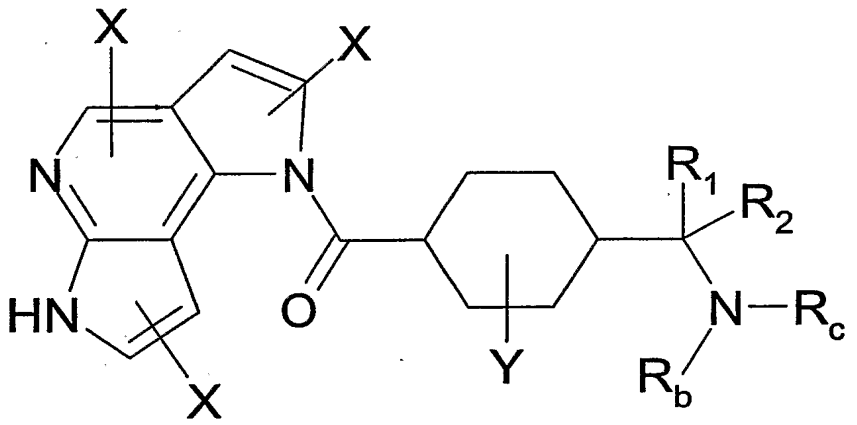
- the distance between the pyridine-nitrogen atom in the group



and the nitrogen atom of the amino group in the group Q, as determined using a Scatter Plot (generated as indicated above), is in the range of 11.0 to 11.8, preferably 11.0 to 11.6, and more preferably 11.0 to 11.4 Angstrom.

Preferred definitions for Ring (3) and the substituents X are as mentioned above; and n and the groups R_1, R_2, R_b and R_c in the group Q are preferably in accordance with the preferences mentioned above for the Alkylene aminogroup (4).

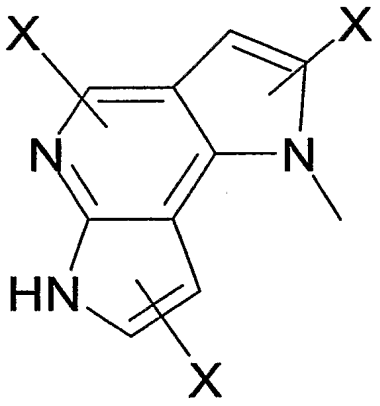
According to one particularly preferred, but non-limiting, aspect of this preferred embodiment, the invention relates to a compound of the formula (XV):



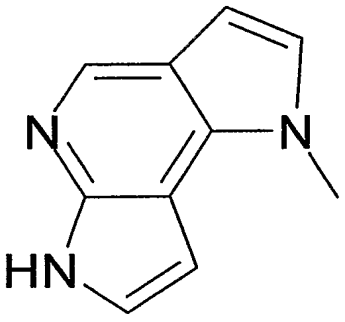
(XV)

in which:

- the group

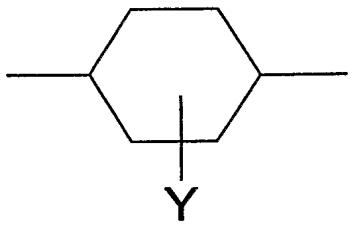


represents a group

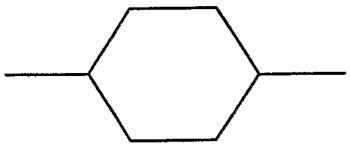


in which each ring may be unsubstituted (i.e. X = hydrogen) or in which any two of the rings or all three of the rings may independently be substituted with 1 or 2 substituents X (and in the case of Ring (1) with only one such substituent X) that are each time independently and suitably chosen from halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, substituted or unsubstituted aryl, nitro, hydroxy and an amino group NR_dR_e (in which R_d and R_e are as defined herein);

- the group



represents a 1,4-cyclohexylene group

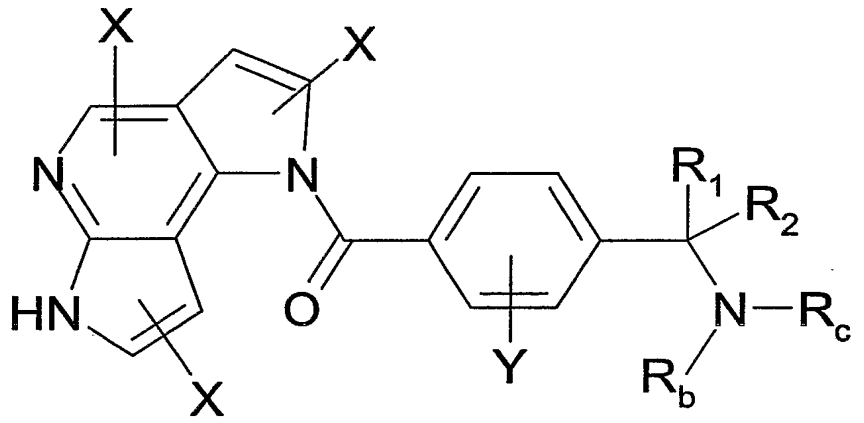


that may be unsubstituted (i.e. Y = hydrogen) or that may be substituted with 1-4, preferably 1 or 2, substituents Y that are each time independently and suitably chosen from halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, substituted or unsubstituted aryl, nitro, hydroxy and an amino group NR_dR_e (in which R_d and R_e are as defined herein);

- R_1, R_2, R_b and R_c are as defined above.

Preferred definitions for the substituents X, the substituents Y, the groups R_1, R_2, R_b and R_c and n are as mentioned above.

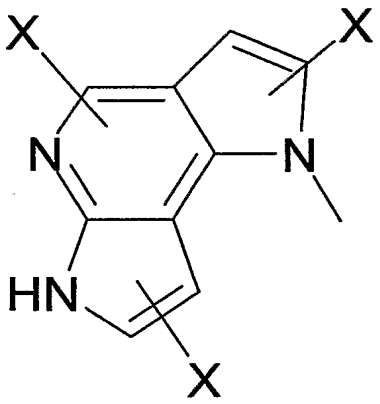
According to one particularly preferred, but non-limiting, aspect of this preferred embodiment, the invention relates to a compound of the formula (XVI):



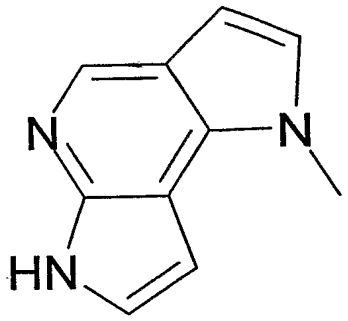
(XVI)

in which:

- the group

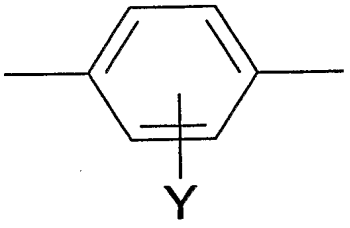


represents a group

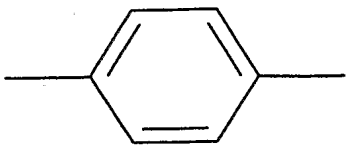


in which each ring may be unsubstituted (i.e. X = hydrogen) or in which any two of the rings or all three of the rings may independently be substituted with 1 or 2 substituents X (and in the case of Ring (1) with only one such substituent X) that are each time independently and suitably chosen from halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, substituted or unsubstituted aryl, nitro, hydroxy and an amino group NR_dR_e (in which R_d and R_e are as defined herein);

the group



represents a 1,4-phenylene group



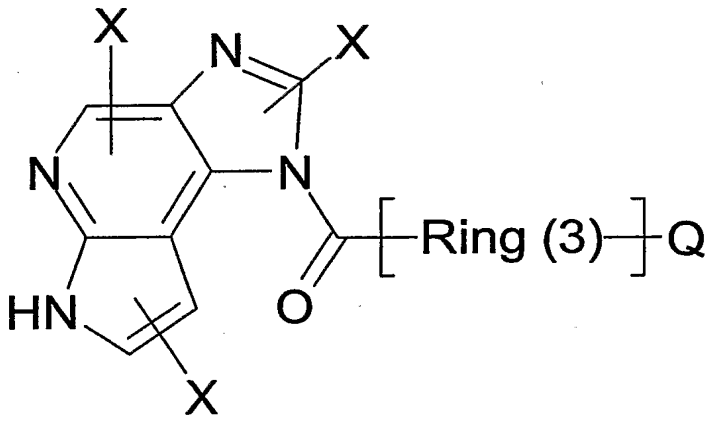
that may be unsubstituted (i.e. Y = hydrogen) or that may be substituted with 1-4, preferably 1 or 2, substituents Y that are each time independently and suitably

chosen from halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, substituted or unsubstituted aryl, nitro, hydroxy and an amino group NR_dR_e (in which R_d and R_e are as defined herein);

- R_1, R_2, R_b and R_c are as defined above.

Preferred definitions for the substituents X, the substituents Y, the groups R_1, R_2, R_b and R_c and n are as mentioned above.

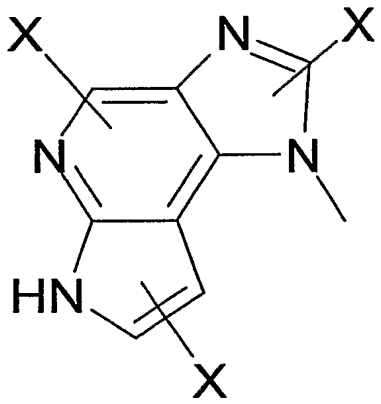
According to one particularly preferred, but non-limiting embodiment, the invention relates to a compound of the formula (XVII):



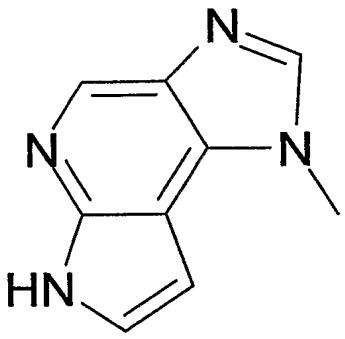
(XVII)

in which:

- the group



represents a group

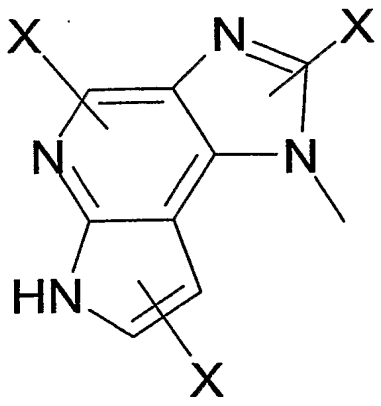


in which each ring may be unsubstituted (i.e. X = hydrogen) or in which any two of the rings or all three of the rings may independently be substituted with 1 or 2 substituents X (and in the case of Rings (1) and (7) with only one such substituent X) that are each time independently and suitably chosen from halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, substituted or unsubstituted aryl, nitro, hydroxy and an amino group NR_dR_e (in which R_d and R_e are as defined herein);

- Ring (3) and Q are as defined above;

and in which:

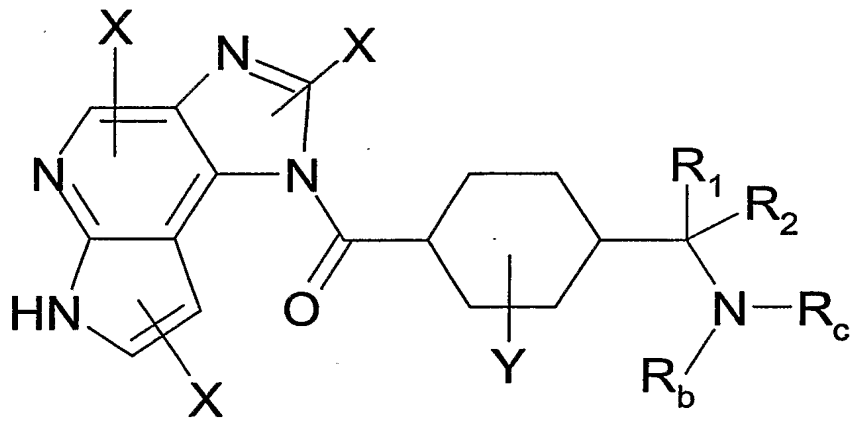
- the distance between the pyridine-nitrogen atom in the group



and the nitrogen atom of the amino group in the group Q, as determined using a Scatter Plot (generated as indicated above), is in the range of 11.0 to 11.8, preferably 11.0 to 11.6, and more preferably 11.0 to 11.4 Angstrom.

Preferred definitions for Ring (3) and the substituents X are as mentioned above; and n and the groups R_1, R_2, R_a and R_c in the group Q are preferably in accordance with the preferences mentioned above for the Alkylene aminogroup (4).

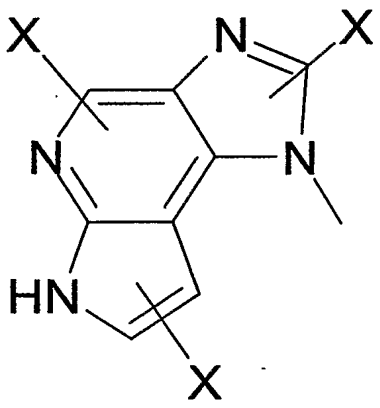
According to one particularly preferred, but non-limiting, aspect of this preferred embodiment, the invention relates to a compound of the formula (XVIII):



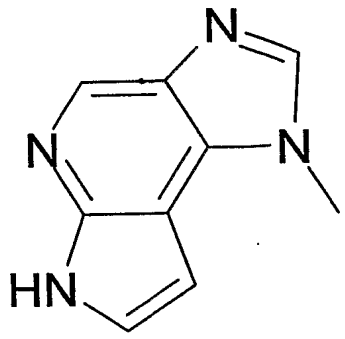
(XVIII)

in which:

- the group

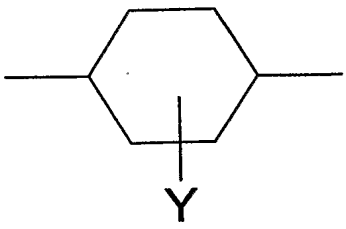


represents a group

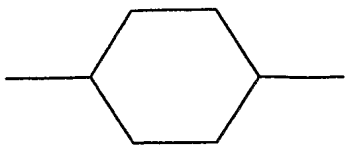


in which each ring may be unsubstituted (i.e. X = hydrogen) or in which any two of the rings or all three of the rings may independently be substituted with 1 or 2 substituents X (and in the case of Rings (1) and (7) with only one such substituent X) that are each time independently and suitably chosen from halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, substituted or unsubstituted aryl, nitro, hydroxy and an amino group NR_dR_e (in which R_d and R_e are as defined herein);

the group



represents a 1,4-cyclohexylene group

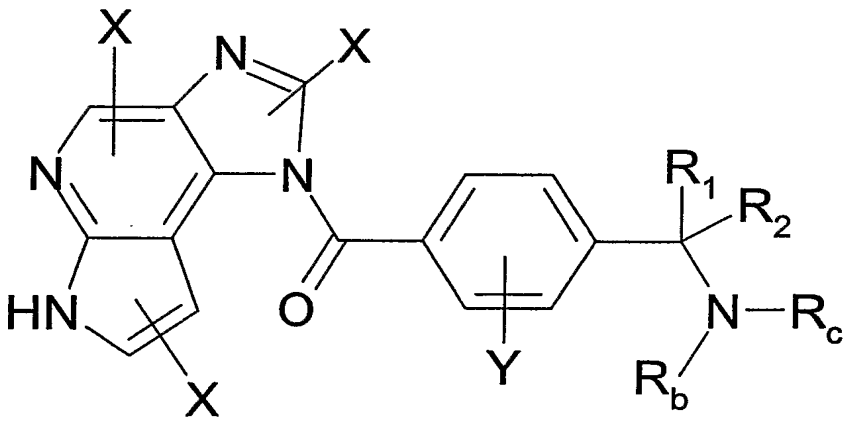


that may be unsubstituted (i.e. Y = hydrogen) or that may be substituted with 1-4, preferably 1 or 2, substituents Y that are each time independently and suitably chosen from halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, substituted or unsubstituted aryl, nitro, hydroxy and an amino group NR_dR_e (in which R_d and R_e are as defined herein);

- R_1, R_2, R_b and R_c are as defined above.

Preferred definitions for R_a, the substituents X, the substituents Y, the groups R_1, R_2, R_b and R_c and n are as mentioned above.

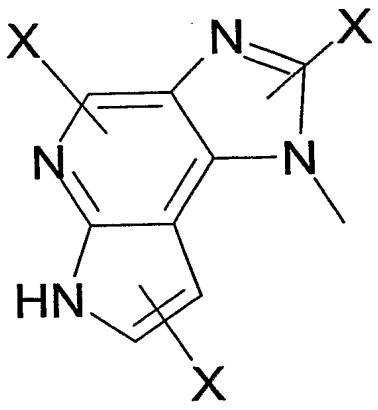
According to one particularly preferred, but non-limiting, aspect of this preferred embodiment, the invention relates to a compound of the formula (XIX):



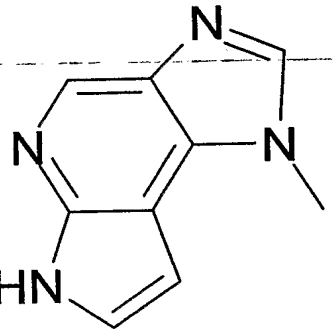
(XIX)

in which:

- the group

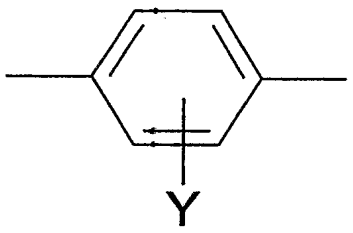


represents a group

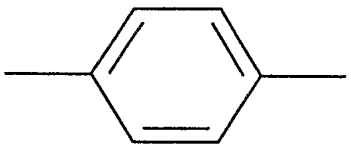


in which each ring may be unsubstituted (i.e. X = hydrogen) or in which any two of the rings or all three of the rings may independently be substituted with 1 or 2 substituents X (and in the case of Rings (1) and (7) with only one such substituent X) that are each time independently and suitably chosen from halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, substituted or unsubstituted aryl, nitro, hydroxy and an amino group NR_dR_e (in which R_d and R_e are as defined herein);

- the group



represents a 1,4-phenylene group



that may be unsubstituted (i.e. Y = hydrogen) or that may be substituted with 1-4, preferably 1 or 2, substituents Y that are each time independently and suitably chosen from halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, substituted or unsubstituted aryl, nitro, hydroxy and an amino group NR_dR_e (in which R_d and R_e are as defined herein);

- R_1, R_2, R_b and R_c are as defined above.

Preferred definitions for the substituents X, the substituents Y, the groups R_1, R_2, R_b and R_c and n are as mentioned above.

In the present description, unless indicated otherwise:

- Halogen refers to fluorine, chlorine, bromine and iodine;
- C_1-C_{10} alkyl includes all linear, branched or cyclic alkyl groups with between 1 and 10 carbon atoms, and thus includes methyl, ethyl, n-propyl, i-propyl, butyl and its isomers (e.g. n-butyl, i-butyl and t-butyl); pentyl and its isomers, hexyl and its isomers, heptyl and its isomers, octyl and its isomers, nonyl and its isomers; decyl and its isomers; and cycloalkyl groups such as cyclopentyl, cyclohexyl, cycloheptyl cyclooctyl, cyclononyl and cyclodecyl (which may be further substituted with one or more alkyl groups such as methyl, ethyl, etc., as long as the total number of carbon atoms is 10 or less); and groups like cyclopentylmethylene and cyclohexylmethylene;

- C_1-C_6 alkyl includes all linear, branched or cyclic alkyl groups with between 1 and 6 carbon atoms, and thus includes methyl, ethyl, n-propyl, i-propyl, butyl and its isomers (e.g. n-butyl, i-butyl and t-butyl); pentyl and its isomers, hexyl and its isomers, cyclopentyl, 2-, 3- or 4-methylcyclopentyl, cyclopentylmethylene, and cyclohexyl.
- C_1-C_{10} alkoxy refers to a group $-OR_c$, in which R_c is C_1-C_{10}alkyl (as defined above).
- C_1-C_6 alkoxy refers to a group $-OR_d$ in which R_d is C_1-C_6alkyl. (as defined above).
- Aryl refers to a substituted or unsubstituted aromatic 5-, 6-, 7- or 8-membered ring containing carbon atoms and optionally 2 or 1 heteroatoms chosen from oxygen, sulfur and nitrogen. Aryl is preferably a 5- or 6-membered ring. Aryl preferably contains only one hetero atom chosen from oxygen, sulfur and nitrogen. The heteroatom is preferably nitrogen. More preferably, aryl is a substituted or unsubstituted 5-membered ring containing carbon atoms and 2, and preferably 1 hetero atom(s), which is most preferably nitrogen; or a substituted or unsubstituted 6-membered aromatic ring containing carbon atoms and 1 and preferably no hetero atoms (i.e. phenyl). The group aryl may also be fused with another substituted or unsubstituted, saturated, unsaturated or preferably aromatic 5-, 6-, 7- or 8- membered, and preferably 5- or 6-membered, ring. Examples of suitable groups aryl will be clear to the skilled person. Most preferably, aryl is substituted or unsubstituted phenyl.
- when a group is said to be "substituted", said group may be substituted with once or more, and preferably once or twice, with substituents chosen from halogen, hydroxy, nitro, cyano, C_1-C_6 alkyl and/or C_1-C_6 alkoxy.

Also, generally, when a carbon atom in a compound of the invention is substituted, it is preferably substituted in such a way that it is bound to only one hetero atom (i.e. other than carbon or hydrogen), it being understood that according to this preferred aspect, carbon atoms that are part of a ring, and in particular of an aromatic ring, may be bound both to a hetero atom that is part of a substituent as well as a hetero atom that is part of the (aromatic) ring.

In the compounds of the invention, R_d and R_e may each independently be one of the groups mentioned for R_b and R_c above (including the structures in which N, R_b and R_c together form a ring), but may also each independently be substituted or unsubstituted

aryl (In this respect, it should be noted that the requirement mentioned above for the amino group -NR_bR_c - i.e. that it is in essentially protonated form at a pH in the range of 5.0 and 9.0 - may, but does not necessarily need to apply to the amino group –NR_dR_e).

The compounds of the invention may be in the form of pharmaceutically and/or veterinary acceptable salts, as generally described below. Particular mention is made of compounds of the Formulas I-XIX above in which a mono-, di or tri-acid addition salt is formed between:

- the at least one hydrogen-accepting hetero atom in Ring (1) and a pharmaceutically acceptable acid; and/or
- the amino group –NR_bR_c and a pharmaceutically acceptable acid; and/or
- any further hydrogen-accepting nitrogen atoms as may be present in Ring (1), Ring (6) or Ring (7);

or any two of these, and preferably all three of these. Some preferred, but non-limiting examples of suitable pharmaceutically acceptable organic and/or inorganic acids are as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, acetic acid and citric acid, as well as other pharmaceutically acceptable acids known per se (for which reference is made to the prior art referred to below).

When the compounds of the invention contain an acidic group as well as a basic group the compounds of the invention may also form internal salts, and such compounds are within the scope of the invention. When the compounds of the invention contain a Ring (6) with a hydrogen-donating hetero atom, the invention also covers salts and/or isomers formed by transfer of said hydrogen atom to a basic group or atom within the molecule.

Also, although generally, with respect to the salts of the compounds of the invention, pharmaceutically acceptable salts are preferred, it should be noted that the invention in its broadest sense also included non-pharmaceutically acceptable salts, which may for example be used in the isolation and/or purification of the compounds of the invention. For example, salts formed with optically active acids or bases may be used to form diastereoisomeric salts that can facilitate the separation of optically active isomers of the compounds of the Formulas I-XIX above.

The invention also generally covers all pharmaceutically acceptable predrugs and prodrugs of the compounds of the Formulas I-XIX above, for which general reference is made to the prior art cited hereinbelow.

Some of the compounds of the invention may contain one or more asymmetric carbon atoms that serve as a chiral center, which may lead to different optical forms (e.g. enantiomers or diastereoisomers). The invention comprises all such optical forms in all possible configurations, as well as mixtures thereof.

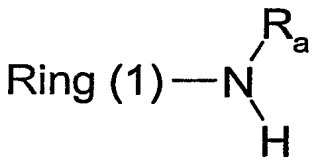
More generally, from the above, it will be clear to the skilled person that the compounds of the invention may exist in the form of different isomers and/or tautomers, including but not limited to geometrical isomers, conformational isomers, E/Z-isomers, stereochemical isomers (i.e. enantiomers and diastereoisomers) and isomers that correspond to the presence of the same substituents on different positions of the rings present in the compounds of the invention. All such possible isomers, tautomers and mixtures thereof are included within the scope of the invention, as long as the distance between the at least one hydrogen-accepting hetero atom in Ring (1) and the nitrogen atom of the Alkylene amino group (4) is within the ranges mentioned above.

Some particularly preferred compounds of the invention are the compounds of Examples 10, 12, 14, 18, 23, 24 and 25, with the compounds of Examples 10, 17, 23, 24 and 25 being particularly preferred.

The compounds of the Formulas I-XIX above may be prepared in a manner known per se for the preparation of analogous compounds, such as the methods described for the preparation of pyridinocarboxamides in US-A-4,997,834 and EP 0 370 498.

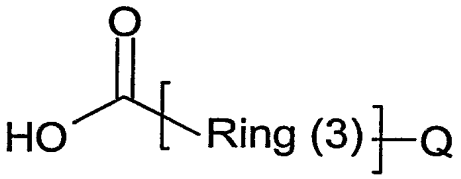
The compounds of the above Formulas I-XIX may be prepared in a manner analogous to methods known per se.

One preferred, but non-limiting method comprises condensation of an amine of formula XX:



(XX)

in which Ring (1) and R_a have the meanings indicated hereinabove, with a carboxylic acid of formula XXI:



(XXI)

in which Ring (3) and Q have the meaning indicated above.

The reaction can generally be performed by coupling the compound of Formula XX with a compound of Formula XXI. IN this reaction, the compound of Formula XXI will usually used as an activated acid derivative thereof, for example as an acyl halogenide that is obtained by converting the compound of Formula XXI into an acyl chloride with thionyl chloride or oxalyl chloride using method known per se. The above reaction can be performed at a suitable molar ratio, for example of between 1:5 and 5:1, preferably between 1:1 and 1:1.5, and most preferably about 1:1; in a suitable solvent or solvent mixture, such as DCM or pyridine, at a suitable temperature, usually between 0°C and the boiling point of the solvent used, such as between room temperature (20°C) and 60°C (depending on the solvent used), and for a suitable period of time, usually between 1 hr and 24 hrs, such as about 1-8 hrs, and in the presence of a suitable base (not in case of pyridine), for example an organic base such as diisoproylethylamine (DIEA), triethylamine (TEA), triisopropylamine, in an amount between 0.1 to 5.0 equivalents.

Alternative conditions for carrying out the above condensation include the use of a coupling agent, such as TBTU, HOBt, or EDCI at a suitable molar ratio, for example between 1;1,0 to 1:3 (relative to the acid derivative); in a suitable solvent or solvent mixture, such as DCM or DMF, at a suitable temperature, usually between 0°C and the

boiling point of the solvent used, such as between room temperature (20°C) and 60°C (depending on the solvent used), and for a suitable period of time, usually between 1 hr and 24 hrs, such as about 1-12 hrs, and in the presence of a suitable base, for example an organic base such as diisoproylethylamine (DIEA), triethylamine (TEA), triisopropylamine, in an amount between 0.1 to 5.0 equivalents.

Other suitable reagents and conditions for performing the above reaction between the amine of Formula XX and the acid XXI (or a suitably activated derivative thereof) will be clear to the skilled person; reference is made to the standard handbooks, such as J. March, Advanced Organic Chemistry, 3rd Edition, 1985.

The starting compounds for this reaction are either commercially available or can be prepared in a manner known per se.

The compounds of the Formulas I-XIX above may then be isolated from the reaction mixture and may optionally be further purified, using techniques known per se, such as evaporation of the solvent, washing, trituration, recrystallization from a suitable solvent or solvent mixture, and chromatographic techniques, such as column chromatography (for example using a silica gel column) or preparative thin layer chromatography. Reference is for example made to the techniques described in the Examples below and to the techniques used in the art for the purification and isolation of analogous compounds, such as the methods for the purification and/or isolation of pyridinocarboxamides described in US-A-4,997,834 and EP 0 370 498.

The compounds of the invention may be used for the inhibition of kinases *in vitro* or *in vivo*, for modulating biological pathways and/or processes in which such kinases are involved; and/or to prevent and/or treat diseases or disorders in which such kinases, pathways and/or processes are involved. For example, the compounds of the invention can be used to inhibit kinases that are involved in metabolic disease, such as JNK1, p38 kinase, GSK-3, IKKbeta (IKappaB kinase beta) and p70S6K, and in particular GSK-3 (compare WO 03/82859); and/or to modulate biological pathways and/or processes in which such kinases are involved.

The compounds of the invention may also be used to inhibit kinases that are (known to be) inhibited by analogous pyridinocarboxamides (for example ROCK); to

modulate biological pathways and/or processes in which such kinases are involved; and/or to prevent and/or treat diseases and disorders associated therewith.

According to one preferred, but non-limiting embodiment, the compounds of the invention may be used to inhibit (at least one isoform of) PKC; and as such may be used for any purposes known per se for inhibitors of PKC.

According to an even more preferred embodiment, the compounds of the invention may be used to inhibit at least one isoform of PKC chosen from the group of calcium-independent, but diacylglycerol- and phorbol ester-sensitive isoforms of PKC, and in particular the delta, epsilon, theta and/or eta isoform of PKC, more in particular the epsilon or theta isoform of PKC; and as such may be used for any purposes known per se for inhibitors of these isoforms.

According to a particularly preferred embodiment, the compounds of the invention are selective for PKC compared to other kinases. By"selective" it is meant that the compound of the invention has an IC_{50} value for one of the PKC isoforms delta, epsilon, eta and/or theta, and in particular for PKC epsilon, that is at least 2 times smaller, preferably at least 5 times smaller, more preferably at least 10 times smaller, such as 50-100 times smaller, than the IC_{50} value for a kinase other than one of the PKC isoforms delta, epsilon, eta and/or theta, and in particular PKC epsilon, as measured using a suitable assay and substrate for measuring the activity of a kinase, such as the assay used in the Examples below, or a similar kinase assay using a suitable substrate. For example, suitable assays and substrates for the various isoforms of PKC are described in the prior art mentioned above and/or are commercially available, such as the Protein Kinase C Assay Kits available from Invitrogen.

According to an even more particularly preferred embodiment, the compounds of the invention are selective for diacylglycerol- and phorbol ester-sensitive isoforms of PKC (e.g. delta, epsilon, theta and/or eta) compared to other isoforms of PKC kinases (e.g. alpha, beta-I, beta-II or gamma). By "selective" it is meant that the compound of the invention has an IC_{50} value for one of the PKC isoforms delta, epsilon, eta and/or theta, and in particular for PKC epsilon, that is at least 2 times smaller, preferably at least 5 times smaller, more preferably at least 10 times smaller, such as 50-100 times smaller, than the IC_{50} value for one of the other PKC isoforms, and in particular PKC gamma, as

measured using a suitable assay and substrate for measuring the activity of a kinase, and in particular for an isoform of PKC, such as the assay used in the Examples below, or a similar kinase assay using a suitable substrate. For example, suitable assays and substrates for the various isoforms of PKC are described in the prior art mentioned above and/or are commercially available, such as the Protein Kinase C Assay Kits available from Invitrogen.

In the invention, particular preference is given to compounds of the Formulas I-XIX above that in the inhibition assay for PKC epsilon described below inhibit PKC epsilon with an IC_{50} value of less than 100 μM, preferably less than 50 μM, more preferably less than 10 μM, even more preferably less than 5 μM, and in particular 1 μM or less, as determined by a suitable assay, such as the assay used in the Examples below.

More particular preference is given to compounds of the Formulas I-XIX above that in the inhibition assay for PKC epsilon described below inhibit PKC epsilon with an IC_{50} value of less than 100 μM, preferably less than 50 μM, more preferably less than 10 μM, even more preferably less than 5 μM, and in particular 1 μM or less; and that inhibit PKC gamma with an IC_{50} value of more than 100 μM, both as determined by a suitable assay, such as the assay used in the Examples below.

The present invention also relates to the use of the compounds of the Formulas I-XIX above in (the preparation of a composition for) inhibiting at least one kinase, in particular for inhibiting at least one isoform of PKC, more in particular for inhibiting the delta, epsilon, eta and/or theta isoform of PKC, and especially for inhibiting the epsilon and/or theta isoform of PKC. Said inhibition may be effected *in vitro* and/or *in vivo,* and when effected *in vivo*, is preferably effected in a selective manner, as defined above.

The compounds of the invention may generally be used for any of the pharmaceutical, veterinary applications of analogous pyridinocarboxamides known per se, such as the pharmaceutical and/or veterinary applications mentioned in US-A-4,997,834 and EP 0 370 498 (e.g. those associated with ROCK).

However, according to a particularly preferred embodiment, the compounds of the invention are preferably used in the prevention and/or treatment of at least one disease or disorder in which at least one isoform of PKC is involved. Such diseases and disorders

will be clear to the skilled person and are for example described in some of the prior art mentioned hereinabove.

According to an even more particularly preferred embodiment, the compounds of the invention may be used in the prevention and/or treatment of at least one disease or disorder in which the delta, epsilon, eta and/or theta isoform of PKC is involved. Such diseases and disorders will be clear to the skilled person and are for example described in some of the prior art mentioned hereinabove.

According to an especially preferred embodiment, the compounds of the invention may be used in the prevention and/or treatment of at least one disease or disorder in which the delta and/or epsilon isoform of PKC is involved. Such diseases and disorders will be clear to the skilled person and are for example described in WO 00/01895, WO 00/01415, US-A-6.376.467, WO 02/102232, US 2003/0134774, WO 03/04612 and some of the further prior art mentioned hereinabove.

For example, the compounds of the invention may be used in the prevention and/or treatment of diseases and disorders such as:

- metabolic diseases, such as:
  (1) hyperglycemic conditions and/or other conditions and/or diseases that are (primarily) associated with (the response or sensitivity to) insulin, including but not limited to all forms of diabetes and disorders resulting from insulin resistance, such as Type I and Type II diabetes, as well as severe insulin resistance, hyperinsulinemia, and hyperlipidemia, e.g., obese subjects, and insulin-resistant diabetes, such as Mendenhall's Syndrome, Werner Syndrome, leprechaunism, lipoatrophic diabetes, and other lipoatrophies;
  (2) conditions caused or usually associated with hyperglycemic conditions and/or obesity, such as hypertension, osteoporosis and/or lipodystrophy;
  (3) so-called "metabolic syndrome" (also known as "Syndrome X") which is a condition where several of the following conditions coexist: hypertension; insulin resistance; diabetes; dyslipidemia; and/or obesity;

  as well as various inherited metabolic diseases known per se; and may also be used also for preventing, treating and/or alleviating complications and/or symptoms associated with these metabolic diseases;

- anxiety, addiction such as alcohol abuse or drug abuse, withdrawal syndrome, muscle spasms, convulsive seizures, epilepsy and other prophylactic and/or therapeutic uses mentioned in WO 00/01895 (for example, to modulate the action of drugs that target the GABA-A receptor)
- pain, such as chronic hyperalgesia, inflammatory pain and the other diseases and disorders mentioned in WO 00/01415, US-A-6.376.467, WO 02/102232, WO 03/089456 and WO 03/089457 and the further prior art listed above;
- heart disease, as mentioned in US 2003/0134774;

and also for regulating the immune system and/or regulating an immune response in a mammal, as mentioned in WO 03/04612.

The compounds of the invention may also be used as an alternative for the peptide inhibitors described in WO 03/089456 and WO 03/089457, e.g. for the same disease indications mentioned in these references for the peptide inhibitors, such as the management of pain. In doing so, the compounds of the invention will have all the usual advantages of small molecules compared to small peptides, for example that they can conveniently be formulated for oral administration, that they are usually easier to manufacture, and that they often are more stable under storage.

In particular, the compounds and compositions of the invention may be used for preventing and/or treating diabetes, especially Type I and Type II diabetes and obesity, as well as the complications and/or symptoms associated therewith. "Diabetes" itself refers to a progressive disease of carbohydrate metabolism involving inadequate production or utilization of insulin and is characterized by hyperglycemia and glycosuria.

In another embodiment, the present invention relates to the use of the compounds of the Formulas I-XIX above in (the preparation of a composition for) the prevention and/or treatment of one or more of the diseases or disorders mentioned above.

In one specific non-limiting embodiment, the present invention relates to the use of the compounds of the Formulas I-XIX above in (the preparation of a composition for) the prevention and/or treatment of metabolic diseases such as diabetes and obesity.

In another specific non-limiting embodiment, the present invention relates to the use of the compounds of the Formulas I-XIX above in (the preparation of a composition

for) the prevention, treatment and/or management of pain, including but not limited to chronic hyperalgesia and inflammatory pain.

For pharmaceutical use, the compounds of the invention may be used as a free acid or base, and/or in the form of a pharmaceutically acceptable acid-addition and/or base-addition salt (e.g. obtained with non-toxic organic or inorganic acid or base), in the form of a hydrate, solvate and/or complex, and/or in the form or a pro-drug or pre-drug, such as an ester. Such salts, hydrates, solvates, etc. and the preparation thereof will be clear to the skilled person; reference is for instance made to the salts, hydrates, solvates, etc. described in US-A-6,372,778, US-A-6,369,086, US-A-6,369,087 and US-A-6,372,733.

Generally, for pharmaceutical use, the compounds of the inventions may be formulated as a pharmaceutical preparation comprising at least one compound of the invention and at least one pharmaceutically acceptable carrier, diluent or excipient and/or adjuvant, and optionally one or more further pharmaceutically active compounds. By means of non-limiting examples, such a formulation may be in a form suitable for oral administration, for parenteral administration (such as by intravenous, intramuscular or subcutaneous injection or intravenous infusion), for topical administration, for administration by inhalation, by a skin patch, by an implant, by a suppository, etc.. Such suitable administration forms - which may be solid, semi-solid or liquid, depending on the manner of administration - as well as methods and carriers, diluents and excipients for use in the preparation thereof, will be clear to the skilled person; reference is again made to for instance US-A-6,372,778, US-A-6,369,086, US-A-6,369,087 and US-A-6,372,733, as well as to the standard handbooks, such as the latest edition of Remington's Pharmaceutical Sciences.

Some preferred, but non-limiting examples of such preparations include tablets, pills, powders, lozenges, sachets, cachets, elixirs, suspensions, emulsions, solutions, syrups, aerosols, ointments, cremes, lotions, soft and hard gelatin capsules, suppositories, sterile injectable solutions and sterile packaged powders (which are usually reconstituted prior to use) for administration as a bolus and/or for continuous administration, which may be formulated with carriers, excipients, and diluents that are suitable per se for such formulations, such as lactose, dextrose, sucrose, sorbitol, mannitol, starches, gum acacia,

calcium phosphate, alginates, tragacanth, gelatin, calcium silicate, microcrystalline cellulose, polyvinylpyrrolidone, polyethylene glycol, cellulose, (sterile) water, methylcellulose, methyl- and propylhydroxybenzoates, talc, magnesium stearate, edible oils, vegetable oils and mineral oils or suitable mixtures thereof. The formulations can optionally contain other pharmaceutically active substances (which may or may not lead to a synergistic effect with the compounds of the invention) and other substances that are commonly used in pharmaceutical formulations, such as lubricating agents, wetting agents, emulsifying and suspending agents, dispersing agents, desintegrants, bulking agents, fillers, preserving agents, sweetening agents, flavoring agents, flow regulators, release agents, etc.. The compositions may also be formulated so as to provide rapid, sustained or delayed release of the active compound(s) contained therein, for example using liposomes or hydrophilic polymeric matrices based on natural gels or synthetic polymers.

Particular reference is made to the compositions, formulations (and carriers, excipients, diluents, etc. for use therein), routes of administration etc., which are known per se for analogous pyridinocarboxamides, such as those described in US-A-4,997,834 and EP-A-0 370 498.

For the treatment of pain, the compounds of the invention may be used locally or systemically, e.g. as described for the peptide inhibitors of PKC in WO 03/089456 and 03/089457. For local administration, the compounds may advantageously be used in the form of a spray, ointment or transdermal patch or another suitable form for topical, transdermal and/or intradermal administration; and for systemic administration, the compounds of the invention may advantageously be administered orally.

The preparations may be prepared in a manner known per se, which usually involves mixing the active substance(s) to be used with the one or more pharmaceutically acceptable carriers, which necessary under aseptic conditions. Reference is again made to US-A-6,372,778, US-A-6,369,086, US-A-6,369,087 and US-A-6,372,733 and the further prior art mentioned above, as well as to the standard handbooks, such as the latest edition of Remington's Pharmaceutical Sciences.

The pharmaceutical preparations of the invention are preferably in a unit dosage form, and may be suitably packaged, for example in a box, blister, vial, bottle, sachet,

ampoule or in any other suitable single-dose or multi-dose holder or container (which may be properly labeled); optionally with one or more leaflets containing product information and/or instructions for use. Generally, such unit dosages will contain between 1 and 1000 mg, and usually between 5 and 500 mg, of the at least one compound of the invention, e.g. about 10, 25, 50, 100, 200, 300 or 400 mg per unit dosage.

The compounds can be administered by a variety of routes including the oral, rectal, transdermal, subcutaneous, intravenous, intramuscular or intranasal routes, depending mainly on the specific preparation used and the condition to be treated or prevented, and with oral and intravenous administration usually being preferred. The at least one compound of the invention will generally be administered in an "effective amount", by which is meant any amount of a compound of the Formulas I-XIX above that, upon suitable administration, is sufficient to achieve the desired therapeutic or prophylactic effect in the individual to which it is administered. Usually, depending on the condition to be prevented or treated and the route of administration, such an effective amount will usually be between 0.01 to 1000 mg, more often between 0.1 and 500 mg, such as between 1 and 250 mg, for example about 5, 10, 20, 50, 100, 150, 200 or 250 mg, per kilogram body weight day of the patient per day, which may be administered as a single daily dose, divided over one or more daily doses, or essentially continuously, e.g. using a drip infusion. The amount(s) to be administered, the route of administration and the further treatment regimen may be determined by the treating clinician, depending on factors such as the age, gender and general condition of the patient and the nature and severity of the disease/symptoms to be treated. Reference is again made to US-A-6,372,778,US-A-6,369,086, US-A-6,369,087 and US-A-6,372,733 and the further prior art mentioned above, as well as to the standard handbooks, such as the latest edition of Remington's Pharmaceutical Sciences.

Thus, in a further aspect, the invention relates to a composition, and in particular a composition for pharmaceutical use, that contains at least one compound of the invention (i.e. a compound that has been identified, discovered and/or developed using a nematode or method as described herein) and at least one suitable carrier (i.e. a carrier suitable for pharmaceutical use). The invention also relates to the use of a compound of the invention in the preparation of such a composition.

It is also envisaged that the above compounds and compositions may be of value in the veterinary field, which for the purposes herein not only includes the prevention and/or treatment of diseases in animals, but also - for economically important animals such as cattle, pigs, sheep, chicken, fish, etc. - enhancing the growth and/or weight of the animal and/or the amount and/or the quality of the meat or other products obtained from the animal. Thus, in a further aspect, the invention relates to a composition for veterinary use that contains at least one compound of the invention (i.e. a compound that has been identified, discovered and/or developed using a nematode or method as described herein) and at least one suitable carrier (i.e. a carrier suitable for veterinary use). The invention also relates to the use of a compound of the invention in the preparation of such a composition.

The invention will now be illustrated by means of the following synthetic and biological examples, which do not limited the scope of the invention in any way. Unless indicated otherwise, the purity of the compounds was confirmed by liquid chromatography/mass spectrometry (LC/MS), as follows:

- HPLC system: Waters 2690 with photodiode array detector Waters 996; Column: C18; Gradient: solvent A (H_2O/formic acid 26.5 nM) 0%, to solvent B (CH_3CN/formic acid 17 nM) 80% in 3 min. Flow: 2.75 ml/min.
- Mass spectrometer: Micromass Platform LC. Ionization: electrospray (polarity:negative and positive).

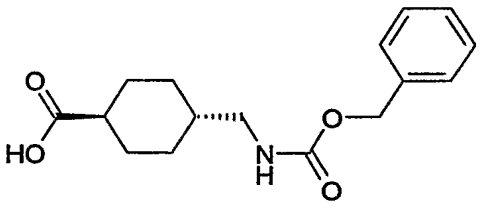
NMR spectra were determined on a Varian Mercury 300 MHz NMR using the indicated solvent as an interal reference. Melting points were determined on a Buechi B-540 and are non-corrected. All reagents used were either obtained commercially or were prepared in a manner known per se.

The Figure shows a Scatter Plot of some of the compounds of the invention and some comparative compounds within the range of 10.8 and 11.8, determined as described above using the commercial software package MOE (Chemical Computing Group, Inc, Quebec, Canada), version 2003.02, on SGI Fuel hardware, running IRIX 6.5, at default parameters (unless indicated otherwise above). Compounds that, in the Biological Examples, have an IC_{50} value for PKC epsilon of less than 100 μM (and thus are considered "active") are shown on the right hand side, and compounds that have an IC_{50}

value for PKC epsilon of more than 100 μM (and thus are considered "inactive") are shown on the left hand side.

Preparation of intermediate compounds:

Intermediate 1: *trans*-4-(benzyloxycarbonylamino-methyl)-cyclohexanecarboxylic acid.

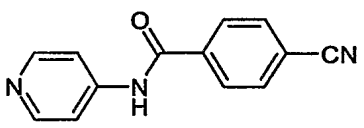


MW=291.35

To a solution of trans-4-methylamino-cyclohexanecarboxylic acid (1 g) in THF (0.25 M), were successively added aqueous 1M Na_2CO_3 (6 ml) and benzyl chloroformate (905 µL, 1.2 eq). The reaction mixture was stirred at RT for 2 days. The solvent was evaporated and the reaction mixture was acidified with 2M HCl (until pH 1-2). The solid was filtered off and washed with water (10ml). The residue was purified by flash chromatography (DCM/MeOH 95/5, R_f=0.29), yielding a white powder (74% yield). ^{1}H NMR (300 MHz, DMSO-d6): 0.83 ppm (m, 2H) ; 1.21 ppm (m, 3H) ; 1.69 ppm (bd, 2H, J=13.0Hz); 1.85 ppm (bd, 2H, J=13.0 Hz); 2.08 ppm (m, 1H) ; 2.82 ppm (t, 2H, J=6.0 Hz);4.98 ppm (s, 2H); 7.32 ppm (m, 6H); 12.02 ppm (s, 1H).

mp: 114.2-116.3°C

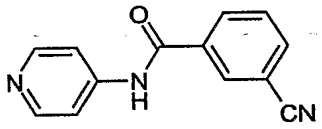
Intermediate 2: 4-cyano-N-pyridin-4-yl-benzamide.



MW=223.24

To a suspension of 4-cyano-benzoic acid (1 g) in DCM (0.5 M) was added oxalyl chloride (2.5 eq) and a few drops of DMF. The reaction mixture was stirred at RT for 15 min. The solvent was evaporated. The residue was dissolved in DCM (0.5 M). DIEA (1.2 eq) and 4-amino-pyridine (640 mg, 1eq) were added. After completion of the reaction (2 hours), the solvent was removed under vacuum. The residue was purified by flash chromatogarphy (DCM/MeOH 95/5, Rf=0.10), yielding a pale yellow powder (42% yield). ^{1}H NMR (300 MHz, DMSO-d6): 7.75 ppm (dd, 2H, J= 1.5 Hz & 4.8 Hz); 8.06 ppm (m, 4H); 8.48 ppm (dd, 2H, J= 1.5 & 4.8Hz); 10.80 ppm (s, 1H).
mp: 200.2-202.4°C.

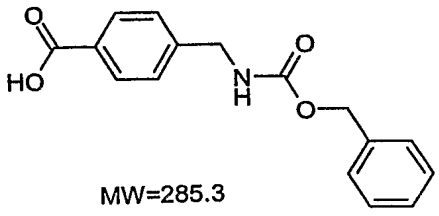
Intermediate 3: 3-cyano-N-pyridin-4-yl-benzamide.



MW=223.24

This compound was prepared according to the procedure of Intermediate 2, starting from 3-cyano-benzoic acid (1.03 g) and 4-amino-pyridine . The title product was purified by flash chromatography (DCM/MeOH 95/5, R_f=0.19), yielding a white powder (54% yield). ^{1}H NMR (300 MHz, DMSO-d6): 7.75 ppm (m, 3H); 8.07 ppm (dt, 1H, J=1.5 & 7.9Hz); 8.23 ppm (dt, 1H, J=1.5 & 7.9Hz); 8.40 ppm (dt, 1H, J=0.6 & 1.8 Hz); 8.49 ppm (dd, 2H, J=1.8 & 5.0 Hz); 10.74 ppm (s, 1H).

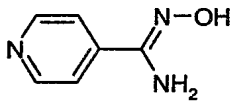
Intermediate 4: 4-(benzyloxycarbonylamino-methyl)-benzoic acid.



MW=285.3

This compound was prepared according to the procedure of Intermediate 1, starting from 4-(aminomethyl)-benzoic acid. The title product was purified by recristallisation in toluene, yielding a white powder (50% yield). ^{1}H NMR (300 MHz, DMSO-d6): 4.30 ppm (d, 2H, J=6.1 Hz); 5.10 ppm (s, 2H); 7.20-7.50 ppm (m, 7H); 7.80-8.10 ppm (m, 3H); 12.90 ppm (s, 1H).
mp: 194.0-195.0°C.

Intermediate 5: Isonicotinamide oxime.

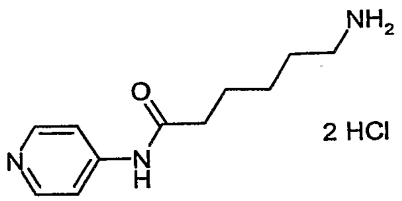


MW=137.14

To a solution of 4-cyano-pyridine (1 g, 9.6 mmol) in absolute EtOH (0.5 M) were added $NH_2OH.HCl$ (1.5 eq) and DIEA (1.6 eq). The reaction mixture was refluxed for 2 hours. The solution was cooled down at RT, and then the solvent was evaporated. The residue was triturated with water. The product was filtered off, washed with water and dried. The title product was obtained as a white powder (77% yield). ^{1}H NMR (300 MHz, DMSO-d6): 6.00 ppm (s, 1H); 7.62 ppm (d, 2H, J=6.2 Hz) ; 8.55 ppm (d, 2H, J=6.2 Hz) ; 10.04ppm (s, 1H).
mp: 193.5-194.9°C

Synthetic Examples:

Example 1 (Comparative): 6-Amino-hexanoic acid pyridin-4-ylamide dihydrochloric acid salt.

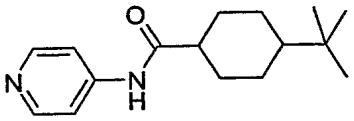


MW =207.28 (+ 2 HCl)

To a solution of 6-*tert*-butoxycarbonylamino-hexanoïc acid (122.8 mg) in DMF (531 µl, 1M), were successively added DIEA (273 µl, 3 eq.) and a solution of TBTU (289 mg) and HOBt (24.3 mg) in DMF (0.5M). After stirring at RT for 3 minutes, 4-aminopyridine (50 mg, 1 eq) was added. The reaction mixture was stirred at RT for 4 hours. The solvent was evaporated and the residue was purified by flash chromatography (DCM/MeOH 9/1, R_f=0.60).

The resulting solid was dissolved in 3N HCl (2.7 ml). The reaction mixture was stirred at 50°C for 3 hr. The reaction mixture was cooled down at RT. The solution was washed with DCM (5 ml). The aqueous layer was evaporated and the residue was triturated in MeoH/Pentane 2/5, yielding a white powder (70% yield). ^{1}H NMR (300 MHz, DMSO-d6): 1.25-1.40 ppm (m, 2H); 1.58 ppm (m, 4H); 2.45-2.55 ppm (m, 2H); 2.45-2.55 ppm (m, 2H); 2.70-2.81 ppm (m, 2H), 7.87 ppm (bs, 2H); 8.08 ppm (d, 2H, J=7.0 Hz); 8.65 ppm (d, 2H, J=7.0 Hz); 11.72 ppm (s, 1H).

Example 2 (Comparative): 4-*tert*-butyl-cyclohexanecarboxylic acid pyridin-4-ylamide.

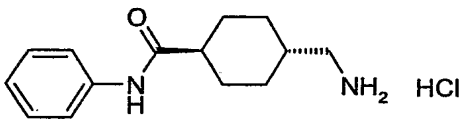


MW =260.38

To a suspension of 4-*tert*-butyl-cyclohexanecarboxylic acid (74 mg) in DCM (0.5 M), was added oxalyl chloride (178 µl, 10eq) and a few drops of DMF. The reaction mixture was stirred at RT for 1 hour. The solvent was evaporated and the residue was dissolved in DCM (0.5 M). To the solution were added pyridine (129 µl 4eq) and 4-aminopyridine (37.7mg, 1 eq). The reaction mixture was stirred at RT overnight. The

solution was washed with aqueous 1M K_2CO_3. The organic layer was evaporated. The residue was purified by flash chromatography (DCM/MeOH 95/5), yielding a white powder (60% yield). ^{1}H NMR (300 MHz, $CDCl_3$): 0.77 ppm (s, 9H); 1.01 ppm (m, 1H); 1.22 ppm (m, 2H); 1.60-1.80 ppm (m, 4H); 2.18 ppm (m, 2H); 2.67 ppm (m, 1H); 7.65 ppm (d, 2H, J=6.2 Hz); 8.07 ppm (bs, 1H); 8.38 ppm (m, 2H, J=6.2 Hz).
mp: 150.0-150.8°C.

Example 3 (Comparative): *Trans*-4-aminomethyl-cyclohexanecarboxylic acid phenylamide hydrochloric acid salt.



MW =232.33 (+HCl)

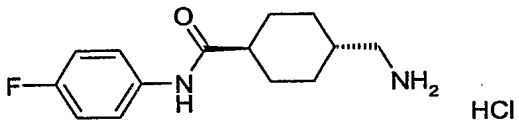
To a solution of Intermediate 1 (114 mg, 1 eq), HOBt (70 mg, 1.3 eq), EDCI.HCl (100 mg, 1.3 eq) and N-methylmorpholine (49 µl, 1.3 eq) in DMF (3 ml) was added aniline (50 µl, 1.3 eq). The reaction mixture was stirred at RT for 24 hours. The solvent was evaporated and the residue was triturated in 2M NaOH. The solid was filtered off and washed with 1M HCl, and then water. The product was purified by flash chromatography (DCM/MeOH 99.5/0.5), yielding the *trans*-(4-phenylcarbamoyl-cyclohexylmethyl)-carbamic acid benzyl ester as a white powder (63% yield).

To a suspension of the solid (91 mg) in MeOH (10 ml) were added Pd (10% on charcoal, 20 mg) and ammonium formate (63 mg, 4 eq). The reaction mixture was stirred at RT overnight. Ammonium formate (1 eq) was added and the reaction miixture was stirred for 24 hours. Pd was removed by filtration, then the solvent was evaporated. The residue was purified by C-18 chromatography. The compound was converted into hydrochloric acid salt (by dissolution in 1M HCl and lyophilisation), yielding a white powder (77% yield). ^{1}H NMR (300 MHz, DMSO-d6): 0.96 ppm (m, 2H); 1.38 ppm (m, 2H); 1.55 ppm (m, 1H); 1.83 ppm (d, 4H, J=10.8 Hz); 2.28 ppm (t, 1H, J=12.1 Hz); 2.64

ppm (t, 2H, J=5.1 Hz); 6.98 ppm (t, 1H, J=7.3 Hz); 7.24 ppm (t, 2H, J=7.3 Hz); 7.58 ppm (d, 2H, J= 7.8 Hz); 7.95 ppm (bs, amine); 9.91 (s, 1H).

mp: 247-249°C

Example 4 (Comparative): *Trans*-4-aminomethyl-cyclohexanecarboxylic acid (4-fluoro-phenyl)-amide hydrochloric acid salt.



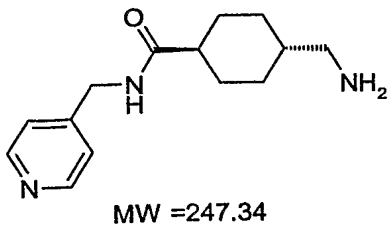
MW =250.32 (+HCl)

The *trans*-[4-(4-fluoro-phenylcarbamoyl)-cyclohexylmethyl]-carbamic acid benzyl ester was obtained in a similar manner as described in Example 3, using Intermediate 1 and 4-fluoro-aniline, yielding a white powder (69% yield).

The title compound was obtained in a similar manner as described in Example 3. A white powder was obtained, after conversion into its hydrochloric acid salt (41% yield). ^{1}H NMR (300 MHz, DMSO-d6): 0.86 ppm (m, 2H); 1.18 ppm (m, 1H); 1.36 ppm (m, 2H); 1.79 ppm (d, 4H, J=11.7 Hz); 2.21 ppm (t, 1H, J=11.7 Hz); 2.37 ppm (d, 1H, J= 6.1 Hz); 2.77 ppm (t, 1H, J= 6.1 Hz); 7.08 ppm (dd, 2H, J=8.7 Hz); 7.58 ppm (dd, 2H, J=8.7 Hz); 9.85 (s, 1H).

mp: 157-159°C.

Example 5 (Comparative): *Trans*-4-aminomethyl-cyclohexanecarboxylic acid (pyridin-4-ylmethyl)-amide.

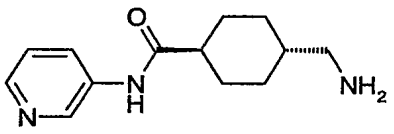


MW =247.34

The *trans*-{4-[(pyridin-4-ylmethyl)-carbamoyl]-cyclohexylmethyl}-carbamic acid benzyl ester was obtained in a similar manner as described in Example 3, using Intermediate 1 and 4-picolylamine. The product was purified by prep-HPLC, yielding a white powder (53% yield).

To a solution of *trans*-{4-[(pyridin-4-ylmethyl)-carbamoyl]-cyclohexylmethyl}-carbamic acid benzyl ester (55 mg) in MeOH (0.1 M) were added Pd/C (6 mg) and ammonium formate (36 mg, 4eq). The reaction mixture was stirred at RT for 4 hours, and then filtered off through a celite cake. The celite was washed with MeOH. The solvent was evaporated, yielding a pale yellow powder (86% yield). ^{1}H NMR (300 MHz, DMSO-d6): 0.87 ppm (m, 2H); 1.20-1.40 ppm (m, 3H); 1.78 ppm (m, 4H); 2.10 ppm (m, 1H); 2.41 ppm (d, 2H, J=6.5 Hz); 4.24 ppm (d, 2H, J=6.2 Hz); 7.18 ppm (d, 2H, J=6.2 Hz); 8.35 (bs, 1H); 8.45 ppm (bd, 2H, J=6.2 Hz).

Example 6 (Comparative): *Trans*-4-aminomethyl-cyclohexanecarboxylic acid pyridin-3-ylamide.



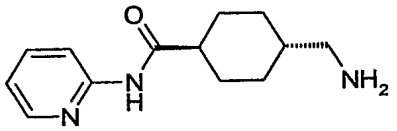
MW =233.32

The *trans*-[4-(pyridin-3-ylcarbamoyl)-cyclohexylmethyl]-carbamic acid benzyl ester was obtained in a similar manner as described in Example 3, using Intermediate 1 and 3-aminopyridine. The product was purified by prep-HPLC, yielding a white powder (25% yield).

The title product was obtained in a similar manner as described in Example 5, yielding a beige powder (10% yield). ^{1}H NMR (300 MHz, DMSO-d6): 0.92 ppm (m, 2H); 1.35-1.45 ppm (m, 3H); 1.82 ppm (m, 4H); 2.30 ppm (m, 1H); 2.58 ppm (d, 2H,

J=6.7 Hz); 7.29 ppm (m, 1H); 8.02 ppm (d, 2H, J=7.8 Hz); 8.20 ppm (d, 2H, J=4.0 Hz); 8.41 ppm (s, 1H); 10.14 ppm (s, 1H).

Example 7 (Comparative): *Trans*-4-aminomethyl-cyclohexanecarboxylic acid pyridin-2-ylamide.

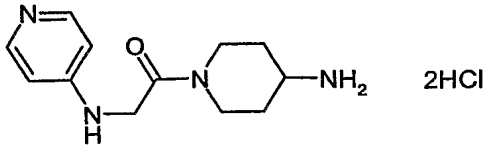


MW =233.32

The *trans*-[4-(pyridin-2-ylcarbamoyl)-cyclohexylmethyl]-carbamic acid benzyl ester was obtained in a similar manner as described in Example 3, using Intermediate 1 and 2-aminopyridine. The product was purified by prep-HPLC, yielding a white powder (15% yield).

The title product was obtained in a similar manner as described in Example 5, yielding a beige powder (10% yield). ^{1}H NMR (300 MHz, DMSO-d6): 0.90 ppm (m, 2H); 1.30-1.40 ppm (m, 3H); 1.70-1.80 ppm (m, 3H); 2.30-2.35 ppm (m, 2H); 2.85-2.95 ppm (m, 2H); 7.04 ppm (m, 1H); 7.72 ppm (m, 1H); 8.05 ppm (d, 1H, J= 8.2 Hz); 8.26 ppm (m, 1H); 10.33 ppm (s, 1H).

Example 8 (Comparative): 4-amino-1-(N-pyridin-4-yl-glycyl)-piperidine dihydrochloric acid salt.

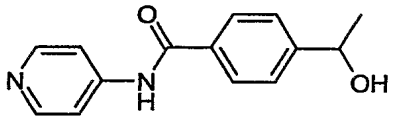


MW=234.30 (+2HCl)

A solution of 4-Boc-amino-piperidine (60 mg), triethylamine (1.1 eq) and DMAP (0.01 eq) in DCM (1.2 ml) was cooled down at 0°C. Bromo-acetyl bromide (1.1 eq) was added, and the reaction mixture was stirred at RT overnight. The solution was washed with water, and then the organic was evaporated. To a solution of the intermediate [1-2(2-bromo-acetyl)-piperidin-4-yl]-carbamic acid *tert*-butyl ester in THF (5 ml) were added DIEA (1 eq) and 4-aminopyridine. The reaction mixture was heated at 50°C overnight. The solvent was evaporated. The residue was dissolved in DCM and washed with water. The organic phase was evaporated, and the product was purified by flash chromatography (DCM/MeOH 90/10), yielding a white powder (93% yield).

The title product was obtained as a white powder (100% yield), after removal of the *tert*-butyloxycarbonyl protecting group under acidic condition. ^{1}H NMR (300 MHz, D_2O): 1.29-1.56 ppm (m, 2H); 1.94 ppm (m, 2H); 2.66 ppm (td, 1H, J= 13.2 and 2.6 Hz); 3.09 ppm (td, 1H, 13.2 and 2.6 Hz); 3.31 ppm (m, 1H); 3.73 ppm (m, 1H); 4.27 ppm (m, 1H); 5.05 ppm (d, 2H, J=2.1 Hz); 6.65 ppm (d, 2H, J=7.6 Hz); 7.62 ppm (d, 2H, J=7.6 Hz).

Example 9 (Comparative): 4-(1-hydroxy-ethyl)-N-pyridin-4-yl-benzamide.

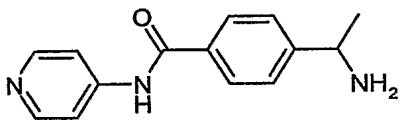


MW=242.28

To a suspension of 4-acetyl-benzoic acid (200 mg) in DCM (0.5 M) was added oxalyl chloride (268 µl, 5 eq) and a few drops of DMF. The reaction was stirred at RT for 1 hour, and then the solvent was evaporated. The residue was dissolved in DCM (0.5 M). Pyridine (100 µl) and 4-aminopyridine (1 eq) were added. The reaction mixture was stirred at RT overnight. The solution was washed with 1M K_2CO_3. The organic phase was evaporated and the residue was purified by flash chromatography (DCM/MeOH 95/5), yielding the 4-acetyl-N-pyridin-4-yl-benzenamide as a white powder (36% yield).

To a solution of the product of step a (157 mg), in water/THF (12 ml/ 2 ml), was added NaBH4 (265 mg, 11 eq). The reaction mixture was stirred at RT for 6 hours. The reaction mixture was acidified by 3M HCl. The solution was washed with DCM (2x10 ml). The aqueous phase was neutralized, and then evaporated, and the residue was purified by flash chromatography, yielding a white powder (64% yield). ^{1}H NMR (300 MHz, DMSO-d6): 1.32 ppm (d, 3H, J= 6.6 Hz); 4.79 ppm (m, 1H); 5.33 ppm (d, 1H, J=4.2 Hz); 7.49 ppm (d, 2H, J=8.2 Hz); 7.76 ppm (d, 2H, J=6.0 Hz); 7.90 ppm (d, 2H, J=8.2 Hz); 8.45 ppm (d, 2H, J=6.0 Hz); 10.52 ppm (s, 1H).

Example 10 (Invention): 4-(1-amino-ethyl)-N-pyridin-4-yl-benzamide.

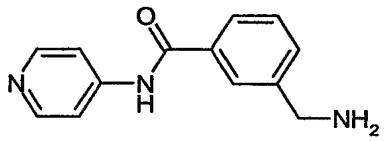


MW=241.30

To a solution of the product of Example 9 (101 mg) in THF (15 ml), were added phtalimide (1.2 eq) and triphenylphosphine (2.4 eq). The reaction mixture was cooled at 0°C, and DEAD (2.4 eq) was added. The solution was stirred at RT for 24 hours. The solvent was evaporated. A mixture AcOEt/pentane 1/1 and 1M HCl were added. The aqueous phase was neutralized by 2M NaOH, and then the product was extracted with DCM. The residue was purified by flash chromatography (DCM/MeOH 95/5, R_f=0.25).

The resulting product was dissolved in EtOH (1 ml). Hydrazine hydrate (1 ml) was added, and the reaction mixture was stirred at 80°C for 1 hour. The reaction mixture was evaporated. The product was partitioned between water and DCM. The aqueous phase was evaporated and the residue was purified by flash chromatography, yielding a white powder (10% yield, after conversion into its dihydrochloric acid salt). ^{1}H NMR (300 MHz, DMSO-d6): 1.51 ppm (d, 3H, J=6.6 Hz); 4.50 ppm (t, 1H, J=6.6 Hz); 7.71 ppm (d, 2H, J=8.4 Hz); 8.13 ppm (d, 2H, J=8.4 Hz); 8.39 ppm (d, 2H, J=6.5 Hz); 8.64 ppm (m, 3H); 8.74 ppm (d, 2H, J=6.5 Hz); 11.81 ppm (s, 1H).

Example 11 (Comparative): 3-aminomethyl-N-pyridin-4-yl-benzamide dihydrochloric acid salt.

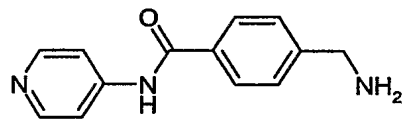


2HCl

MW=227.27 (+2HCl)

To a solution of Intermediate 3 (50 mg) in MeOH (2 ml), was added cobalt (II) chloride hexahydrate (1.2 eq) and MeOH (2 ml). $NaBH_4$ (3x8 eq) were then added (in 4 hours). The blue solution turned into a black suspension. The reaction mixture was stirred at RT for 4 hours. The reaction mixture was filtered through celite. The celite cake was washed with MeOH. The solvent was evaporated and the product was partitioned between DCM and water. The organic phase was washed with water, then concentrated. The residue was purified by C-18 chromatography, yielding a white solid (22% yield, after conversion into its dihydrochloric acid salt). ^1H NMR (300 MHz, DMSO-d6): 4.19 ppm (m, 2H); 7.64 ppm (m, 1H); 7.81 ppm (m, 1H); 78.08 ppm (d, 2H, J=7.1 Hz); 8.35 ppm (m, 2H); 8.40 ppm (m, 3H); 8.75 ppm (d, 2H, J=6.2 Hz); 9.09 ppm (bs,1H); 11.72 ppm (s, 1H).

Example 12 (Invention): 4-aminomethyl-N-pyridin-4-yl-benzamide dihydrochloric acid salt.



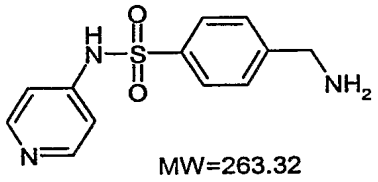
2HCl

MW=227.27 (+2HCl)

The title product was obtained in a similar manner as described in Example 11, starting from Intermediate 2, yielding a white powder after conversion into its

dihydrochloric acid salt (24% yield). ^{1}H NMR (300 MHz, DMSO-d6): 4.13 ppm (broad d, 2H); 7.67 ppm (d, 2H, J=8.5 Hz); 8.10 ppm (d, 2H, J=8.5 Hz); 8.33 ppm (d, 2H, J=6.7 Hz); 8.45 ppm (bs, 3H); 8.73 ppm (d, 2H, J=6.7 Hz). 11.65 ppm (s, 1H).

Example 13 (Comparative): 4-aminomethyl-N-pyridin-4-yl-benzenesulfonamide.

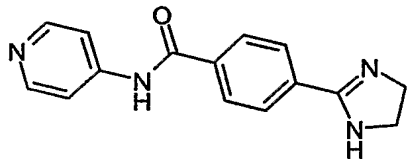


MW=263.32

To a solution of 4-aminopyridine (100 mg) in DMF (0.2 M) were added DIEA (1.1 eq) and a solution of 4-cyano-benzenesulfonyl chloride (47 mg, 1 eq) in THF (0.25 M). The reaction mixture was stirred at RT for 4 hours. The solvent was evaporated and the residue was purified by prep-HPLC.

The 4-cyano-N-pyridin-4-yl-benzenesulfonamide (60 mg) was dissolved in THF (0.22 M). A 1M solution of BH3 in THF (5 eq) was carrefully added. The reaction mixture was stirred at 30°C for 0.5 hour. 3N HCl (3.6 eq) was then added and the reaction mixture was refluxed for 0.5 hour. The reaction mixture was cooled down at 0°C and NaOH was added (7.2 eq). The solution was saturated with potassium carbonate and extracted with DCM. The compound was not detected in the organic phase. The aqueous layer was evaporated and the residue was purified by flash chromatography (DCM/MeOH/NH_3 sat. 90/10 to 75/25), yielding a yelow powder (32% yield). ^{1}H NMR (300 MHz, DMSO-d6): 3.69 ppm (bs, 2H); 6.57 ppm (d, 2H, J= 6.1 Hz); 7.28 ppm (m, 2H); 7.51 ppm (d, 1H, J=8.2 Hz); 7.61 ppm (d, 2H, J=8.2 Hz); 7.79 ppm (d, 2H, J=6.1 Hz).

Example 14 (Invention): 4-(4,5-dihydro-1H-imidazol-2-yl)-N-pyridin-4-yl-benzamide.

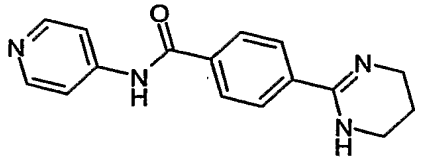


MW=266.31

A mixture of Intermediate 2 (50 mg), 1,2-ethylenediamine (1 g, 75 eq) and P_4S_{10} (7 mg, 0.07 eq) was heated at 90°C for 2 hours. The reaction mixture was cooled down at RT. The 1,2-ethylenediamine in excess was evaporated under vacuum. Water (3 ml) was then added and the reaction mixture was stirred at RT until the yellow color disappeared. The precipitate was filtered off and washed with water, yielding a white powder (58% yield). ^{1}H NMR (300 MHz, DMSO-d6): 3.33 ppm (s, 2H); 3.62 ppm (s, 2H); 6.87 ppm (bs, 1H); 7.77 ppm (d, 2H, J=5.9 Hz); 7.95 ppm (m, 4H); 8.47 ppm (d, 2H); 10.65 ppm (s, 1H).

mp >250°C

Example 15 (Comparative): N-pyridin-4-yl-4-(1,4,5,6-tetrahydro-1H-pyrimidin-2-yl)-benzamide.

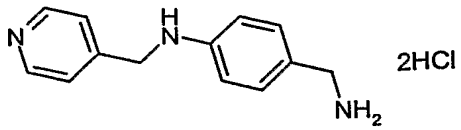


MW=280.33

This compound was obtained in a similar manner as described in Example 14 using Intermediate 2 and 1,3-diaminopropane, yielding a white powder (42% yield). ^{1}H NMR (300 MHz, DMSO-d6): 1.68 ppm (m, 2H); 3.35 ppm (4H in the signal of water); 7.77 ppm (d, 2H, J= 6.0 Hz); 7.88 ppm (d, 2H, J= 8.5 Hz); 7.95 ppm (d, 2H, J= 8.5 Hz); 8.46 ppm (d, 2H, J=6.0 Hz); 10.62 (bs, 1H).

mp: 277.6-278.7°C.

Example 16 (Comparative): (4-aminomethyl-phenyl)-pyridin-4-ylmethyl-amine dihydrochloric acid salt.

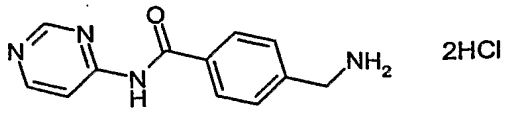


MW=213.28 (+2HCl)

To a mixture of pyridine-4-carbaldehyde (44 mg, 1 eq) and (4-amino-benzyl)-carbamic acid *tert*-butyl ester (1.1 eq) in DCM (0.3 M) at 0°C, was added $NaBH(OAc)_3$ (130 mg). The reaction mixture was stirred at RT overnight. The solvent was evaporated, and the residue purified by prep-HPLC, yielding {4-[(pyridin-4-ylmethyl)-amino]-benzyl}-carbamic acid *tert*-butyl ester as a white powder (57% yield). 1H NMR (300 MHz, DMSO-d6): 1.34 ppm (s, 9H); 3.90 ppm (d, 2H, J=6.2 Hz); 4.27 ppm (d, 2H, J=5.9 Hz); 6.28 ppm (t, 1H, J=6.2 Hz); 6.44 ppm (d, 2H, J=8.5 Hz); 6.89 ppm (d, 2H, J=8.5 Hz); 7.14 ppm (t, 1H, J=5.9 Hz); 7.29 ppm (dd, 2H, J=4.4 and 1.5 Hz); 8.44 ppm (dd, 2H, J=4.4 and 1.5 Hz).

The product was dissolved in 3M HCl. The solution was heated at 80°C for 2 hours. The solvent was evaporated, yielding the title product as a white solid (100%yield). 1H NMR (300 MHz, DMSO-d6): 3.74 ppm (d, 2H, J=5.6 Hz); 4.60 ppm (s, 2H); 6.54 ppm (d, 2H, J=8.5 Hz); 7.18 ppm (d, 2H, J=8.5 Hz); 7.95 ppm (d, 2H, J=6.8 Hz); 8.41 ppm (bs, 2H); 8.84 ppm (d, 2H, J=8.5 Hz).

Example 17 (Comparative): 4-aminomethyl-N-pyrimidin-4-yl-benzamide dihydrochloric acid salt.

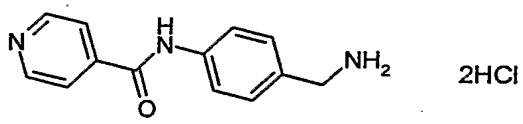


MW=228.26 (+2HCl)

A solution of Intermediate 4 (50 mg) in thionyl chloride (1 ml) heated at 40 °C for 2.5 hours. The solution was cooled down to RT, and then evaporated under vacuum. The resulting solid was dissolved in DCM (0.2 ml) and the solution was added dropwise to a solution of 4-aminopyrimidine (16.7 mg, 1 eq) in pyridine (1 ml, 0.17 M). After stirring at 100 °C for 1 hour, the reaction mixture was cooled down to RT, and then evaporated under vacuum. The resulting solid was dissolved in DCM. The organic layer was washed with 1M K_2CO_3, with water, dried ($MgSO_4$) and evaporated under vacuum, yielding the [4-(pyrimidin-4-ylcarbamoyl)-benzyl]-carbamic acid benzyl ester as an orange powder (43% yield).

To a solution of [4-(pyrimidin-4-ylcarbamoyl)-benzyl]-carbamic acid benzyl ester (27 mg), in methanol (5 ml), was added ammonium formate (37.6 mg, 8 eq) and Pd/C-10 % (5 mg). After 6 hours stirring at RT, the mixture was filtered through a celite cake and the filtrate evaporated under vacuum. The residue was dissolved in HCl 1N, the aqueous layer was washed with DCM, and then evaporated under vacuum, yielding a beige powder (27% yield). ^{1}H NMR (300 MHz, DMSO-d6): 4.20 ppm (m, 2H); 7.68 ppm (d, 2H, J=8.2 Hz); 8.15 ppm (d, 2H, J=8.2 Hz); 8.30 ppm (d, 2H, J=5.3 Hz); 8.42 ppm (m, 3H); 8.82 ppm (m, 1H); 9.06 ppm (s, 1H); 11.4 Angstrom2 ppm (s, 1H).

Example 18 (Invention): *N*-(4-aminomethyl-phenyl) isonicotinamide dihydrochloric acid salt.



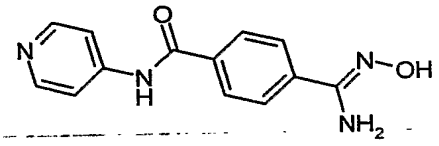
MW=227.27 (+2HCl)

To a suspension of isonicotinic acid (100 mg) in DCM (0.25 M) were added oxalyl chloride and 1 drop of DMF. The reaction mixture was stirred at RT for 3 hours, and then evaporated. To a solution of isonicotinyl chloride in DCM (3 ml), was added a solution of (4-amino-benzyl)-carbamic acid tert-butyl ester (prepared by known method, 1 eq) and DIEA (3 eq) in DCM (3 ml). The reaction mixture was stirred at RT for 1 hour.

The solution was diluted with DCM, and then washed with 1M K2CO3 and brine. The organic layer was dried (over MgSO4) and evaporated.

The residue was dissolved in 3M HCl. The solution was heated at 50°C for 2 hours, cooled down at RT, and then evaporated, yielding a yellow powder (59% yield). ^{1}H NMR (300 MHz, DMSO-d6): 3.97 ppm (m, 2H); 7.48 ppm (d, 2H, J=8.5 Hz); 7.82 ppm (d, 2H, J=8.5 Hz); 8.18 ppm (d, 2H, J=6.2 Hz); 8.39 ppm (m, 3H); 8.93 ppm (d, 2H, J=6.2 Hz); 10.96 ppm (s,1H).

Example 19 (Comparative): 4-(*N*-pyridin-4-yl)-benzamide oxime.

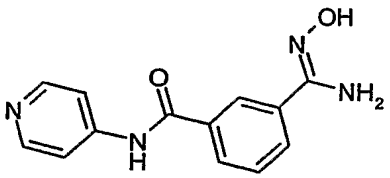


MW=256.27

To a suspension of Intermediate 2 (48 mg), in EtOH (0.5 M), were added $NH_2OH.HCl$ (1.5 eq) and DIEA (1.6 eq). The reaction mixture was refluxed for 2.5 hours. The reaction mixture was cooled down at RT. The solvent was evaporated. The product was triturated with water, filtered off and washed with water. The product was dried, yielding a pale yellow powder (90% yield). ^{1}H NMR (300 MHz, DMSO-d6): 6.24 ppm (bs, 2H); 7.85 ppm (d, 2H, J=8.2 Hz); 8.03 ppm (m, 4H); 8.58 ppm (d, 2H, J=6.4 Hz); 10.02 ppm (bs, 1H); 11.12 ppm (s, 1H).

mp: 233.5-235.8°C.

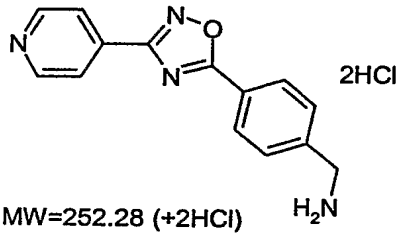
Example 20 (Comparative): 3-(*N*-pyridin-4-yl)-benzamide oxime.



MW=256.27

This compound was obtained in a similar manner as described in Example 19, using Intermediate 3, yielding a white powder (76%yield). ^{1}H NMR (300 MHz, DMSO-d6): 5.94 ppm (s, 2H); 7.54 ppm (t, 1H, J=7.7 Hz); 7.76 ppm (d, 2H, J=5.4 Hz); 7.89 ppm (m, 2H); 8.23 ppm (s, 1H); 8.47 ppm (bs, 2H); 9.76 ppm (s, 1H); 10.64 ppm (s, 1H).

Example 21 (Comparative): 4-(3-pyridin-4-yl-[1,2,4]oxadiazol-5-yl-benzylamine dihydrochloric acid salt.



MW=252.28 (+2HCl)

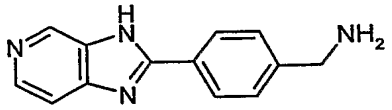
To a solution of 4-(Boc-aminomethyl)-benzoic acid (187 mg) in DMF (0.25 M) were added DIEA (5 eq), TBTU (1 eq) and HOBt (0.2 eq). The solution was stirred at RT for 3 minutes, and then Intermediate 5 (102mg, 1 eq) was added. After 1 hour, the solvent was evaporated. The residue was triturated with 0.05 M NaOH (5 ml). The solid was filtered off, washed with water and dried under vacuum.

The solid was dissolved in DMF (0.25 M). The reaction mixture was heated at 110°C for 2 hours. The reaction mixture was cooled down at RT. The precipitate was filtered off, washed with water, and then dried under vacuum.

The solid was dissolved in 3N HCl. The solution was heated at 50°C for 2 hours. The solvent was evaporated and the residue was dried under vacuum. The title product was obtained as a white powder (74% yield). ^{1}H NMR (300 MHz, DMSO-d6): 4.15 ppm

(q, 2H,J=5.7 Hz); 5.00 ppm (bs, 2H); 7.80 ppm (d, 2H, J=8.4 Hz); 8.24 ppm (m, 4H); 8.95 ppm (d, 2H, J=6.0 Hz).

Example 22 (Comparative): 4-(3*H*-imidazo[4,5-*c*]pyridin-2-yl)-benzylamine.

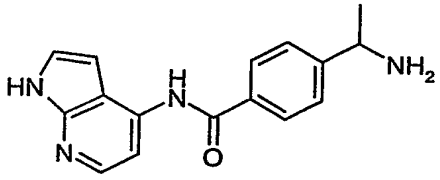


MW=224.27

A solution of 3,4-Diaminopyridine (200 mg) and 4-cyanobenzonitrile (240 mg; 1 eq) in DMF (18.3 ml; 0.1M) was heated at 100°C for 48 hours. The reaction mixture was cooled down at RT. The precipitate was filtered off, washed with DMF and water. The 4-(3*H*-imidazo[4,5-*c*]pyridin-2-yl)-benzonitrile was purified by flash chromatography (DCM/MeOH 98/2), yielding a white powder (64% yield).

To a solution of 4-(3*H*-imidazo[4,5-*c*]pyridin-2-yl)-benzonitrile (100 mg), in methanol (2.5 ml), was added cobalt (II) chloride hexahydrate (26.3 mg; 2.4 eq). The reaction mixture was cooled at 0°C and $NaBH_4$ (209 mg, 12 eq) was added portionwise. After stirring overnight at RT, cobalt (II) chloride hexahydrate (26.3 mg; 2.4 eq) and $NaBH_4$ (209 mg, 12 eq) were added and the reaction stirred at RT for 4 hours. The medium was then filtered through a celite cake and the filtrate was evaporated under vacuum. The crude solid was dissolved in DCM and the organic layer extracted 3 times with water. The aqueous layers were combined and evaporated under vacuum. The residue was purified by flash chromatography (DCM/MeOH/TEA 90/9/1), yielding a white powder (63% yield). ^{1}H NMR (300 MHz, DMSO-d6): 4.05 ppm (m, 2H); 7.58 ppm (d, 2H, J=5.6 Hz); 7.65 ppm (d, 2H, J=7.7 Hz); 8.25 ppm (d, 2H, J=7.7 Hz); 8.29 ppm (d, 2H, J=5.6 Hz); 8.92 ppm (s,1H).

Example 23 (Invention): 4-(1-amino-ethyl)-*N*-(1*H*-pyrrolo[2,3-*b*]pyridin-4-yl)-benzamide.

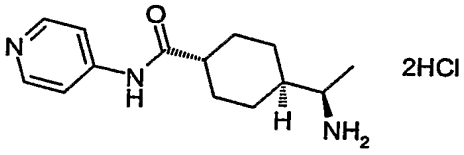


MW=280.33

A solution of 4-(1-benzyloxycarbonylamino-ehyl)-benzoic acid (225 mg) was heated at 50°C overnight. The reaction mixture was evaporated, and then the residue was dried. To a solution of 1H-pyrrolo[2,3-b]pyridin-4-ylamine (100 mg, 1eq) in pyridine was added the 4-(1-benzyloxycarbonylamino-ehyl)-benzoyl chloride, dissolved in a minimum of DCM. The resulting solution was heated at 50°C for 2 hours. The reaction mixture was cooled down at RT, and then evaporated. The residue was purified by prep-HPLC, yyielding the {1-[4-(1H-pyrrolo[2,3-b]pyridin-4-ylcarbamoyl)-phenyl]-ethyl}-carbamic acid benzyl ester as a white powder (32% yield).

The title product was obtained in a similar manner as described in Example 5, yielding a white powder (10% yield). ^{1}H NMR (300 MHz, DMSO-d6): 1.33 ppm (d, 3H, J=6.9 Hz); 4.18 ppm (q, 1H, J=6.9 Hz); 6.79 ppm (dd, 1H, J=3.5 and 1.5 Hz); 7.36 ppm (broad t, J=3.5 Hz); 7.56 ppm (d, 2H, J=8.1 Hz); 7.68 ppm (d, 1H, J=5.4 Hz); 7.94 ppm (d, 2H, J=8.1 Hz); 8.14 ppm (d, 1H, J=5.4 Hz); 10.29 ppm (s, 1H); 11.57 ppm (s, 1H).

Example 24 (Invention): (R)-(+)-*trans*-N-(4-pyridyl)-4-(1-aminoethyl)-cyclohexanecarboxamide



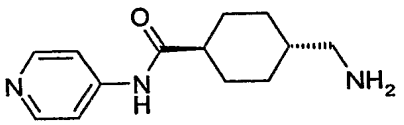
2HCl

MW=247.34 (+2HCl)

Y-27632 dihydrochloride

This compounds was obtained from CALBIOCHEM (Compound Y 27632, Cat. No. 688000).

Example 25 (Invention): *Trans*-4-aminomethyl-cyclohexanecarboxylic acid pyridin-4-ylamide.



MW =233.32

The *trans*-[4-(pyridin-4-ylcarbamoyl)-cyclohexylmethyl]-carbamic acid benzyl ester was obtained in a similar manner as described in Example 3, using Intermediate 1 and 4-aminopyridine, yielding after purification by flash chromatography (DCM/MeOH 97/3), a white powder (15% yield).

The title compound was obtained in a similar manner as described in Example 3. A white powder was obtained (50% yield). ^{1}H NMR (300 MHz, DMSO-d6): 0.88-0.96 ppm (m, 2H); 1.20-1.46 ppm (m, 3H); 1.83 ppm (m, 3H); 2.30 ppm (m, 1H); 2.58 ppm (d, 2H, J=6.7 Hz); 2.94 ppm (d, 1H, J= 7.5 Hz); 7.55 ppm (d, 2H, J=5.7 Hz); 8.36 ppm (d, 2H, J=5.7 Hz); 8.40 (bs, 2H); 10.37 (s, 1H).

Biological Examples:

The compounds of Examples 1-25 tested for inhibition of the PKC isoforms PKC epsilon, PKC gamma, PKC theta and PKC zeta.

The inhibition assays were performed with a fluorescence polarization (FP) assay using the commercially available Protein Kinase C Assay Kit, Red, from Invitrogen (Product ID. No. P2941), essentially in accordance with the protocol supplied by the manufacturer. The substrate used was RFARKGLRQKNV (M_w 11561), also obtained from Invitrogen (Product ID No. P2760). The isozymes PKC epsilon, PKC gamma, PKC

theta and PKC zeta were also obtained from Invitrogen (Product ID Nos: P2282, P2228, P2996 and P2273).

In summary, all compounds were screened in the wells of a 384 well plate for inhibition of each of the isozymes at 20 concentrations in the range of 100μM – 2pM using a stepwise 2-fold dilution. Staurosporine was used as a reference (2 μM for PKC epsilon, gamma and theta and 40 μM for PKC zeta).

To perform the assay, 2 μl of a solution of the compound to be tested in DMSO (at each concentration) was added to 6 μl of a solution of the enzyme in 10 mM HEPES, 5 mM dithiotreitol, 0.1% Triton X-10, pH 7,4. The final concentration of the enzymes were 10 ng/ml for PKC epsilon and 20 ng/ml for PKC gamma, theta and zeta.

After incubating for 30 minutes at room temperature, 4 μl of a mixture of ATP and the protein substrate in 20mM HEPES (pH7.4), 5mM $MgCl_2$, 5mM $CaCl_2$, 0.02% NP40 was added. The final concentration of the ATP was 2.5 μM and final concentration of protein substrate was 1 μM.

After incubating for 80 minutes at room temperature, 3 μl of a mix solution of 500 mM EDTA (stop solution) and the Rhodamine-based PKC Red Tracer (from the Protein Kinase C Assay Kit) in BGG/phosphate buffer (pH7.4) with 0.02% NaN and 0.1% Triton X-100 was added and 5 μl of a the Anti-Phosphoserine antibody (also from the Protein Kinase C Assay Kit) in BGG/phosphate buffer (pH7.4) with 0.02% NaN.

The mixture thus obtained (total volume: 20 μl) was incubated for 60 minutes at room temperature, upon which the fluorescence polarization was measured using an automated plate reader (Perkin Elmer, Model Envision 2100-0010 HTS) with FP filters for rhodamine: excitation filter FITC FP 531 and emission filters FITC FP P-pol 595 and FITC FP S-pol 595 (Perkin-Elmer).

The results were fitted to a curve using the XL-Fit algorithm and IC_{50} values were calculated for each fitted curve, again using the XL-Fit algorithm.

The results for the compounds tested are shown in the Table below. Examples 1-9, 11, 13, 15-17 and 22 are Comparative Examples; Examples 10, 12, 14, 18, 23, 24 and 25 are examples of compounds of the invention, with the compounds of Examples 10, 17, 23, 24 and 25 being particularly preferred. In Table 1, "MW" indicates the molecular weight, and "D" indicates the distance between the pyridine-nitrogen atom and the

nitrogen atom in the amino group, as determined by Scatter Plot (as described above). Where no value for the distance is mentioned, the

The IC_{50} values for the reference, staurosporine, were 0.045μM for PKC epsilon, 0.02μM for PKC gamma, 0.05μM for PKC theta and 1μM for PKC zeta.

In Table 1, "MW" indicates the molecular weight, and "D" indicates the distance between the pyridine-nitrogen atom and the nitrogen atom in the amino group, as determined by Scatter Plot (as described above). For the compounds of Examples 2-4, no distance could be determined, as these compounds do not contain a pyridine-nitrogen.

TABLE 1

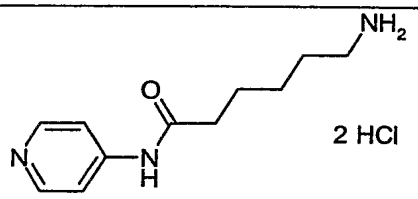
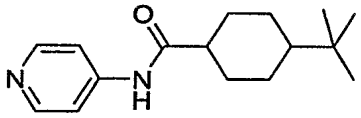
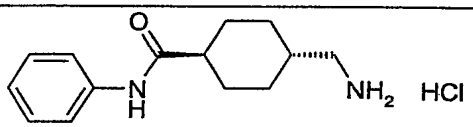
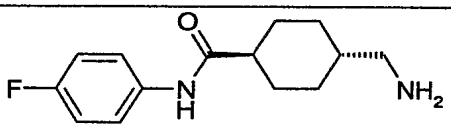
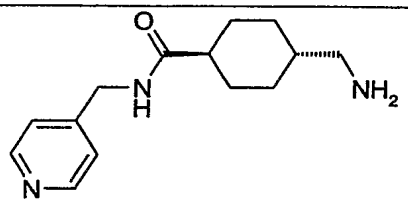
Ex	Formula	IC_{50} μM			
		PKCε	PKCγ	PKCθ	PKCζ
1	 2 HCl MW =207.28 (+ 2 HCl) D = 10.93	>100	>100	>100	>100
2	 MW =260.38	>100	>100	>100	>100
3	 HCl MW =232.33 (+HCl)	>100	90.5	>100	40.3
4	 HCl MW =250.32 (+HCl)	>100	>100	>100	>100
5	 MW =247.34 D = 11.76	>100	>100	>100	>100

TABLE 1 (Continued)

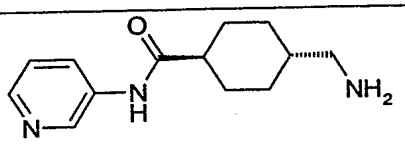
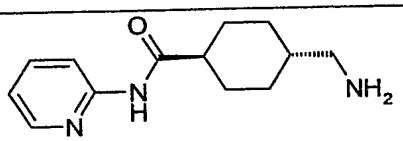
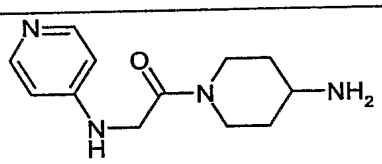
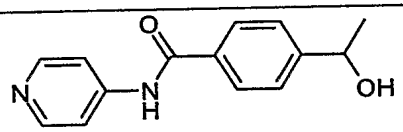
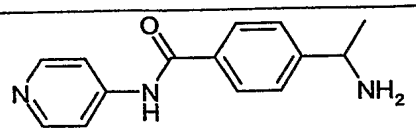
Ex	Formula	IC_{50} μM			
		PKCϵ	PKCγ	PKCθ	PKCζ
6	 MW =233.32 D = 6.75	>100	>100	>100	>100
7	 MW =233.32 D = 8.82	>100	>100	>100	>100
8	 3HCl MW=234.30 (+3HCl) D = 8.75	>100	>100	>100	>100
9	 MW=242.28 D = 11.07	>100	>100	>100	>100
10	 MW=241.30 D = 11.16	1.21	>100	2.25	22.14

TABLE 1 (Continued)

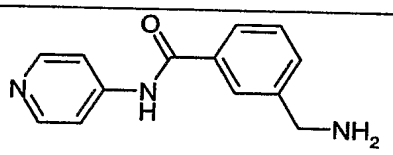
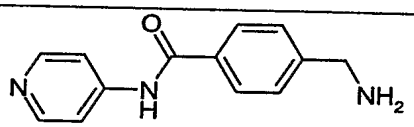
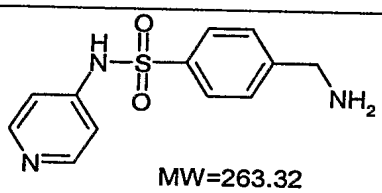
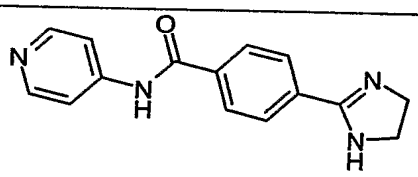
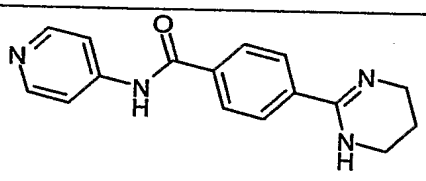
Ex	Formula	IC_{50} μM			
		PKCϵ	PKCγ	PKCθ	PKCζ
11	 MW=227.27 D = 10.87	>100	>100	>100	>100
12	 MW=227.27 D = 11.13	6.23	>100	9.14	51.40
13	 MW=263.32 D = 6.06	>100	>100	>100	>100
14	 MW=266.31 D = 11.64	61.97	>100	53.48	>100
15	 MW=280.33 D = 11.12	>30	>30	>30	>30

TABLE 1 (Continued)

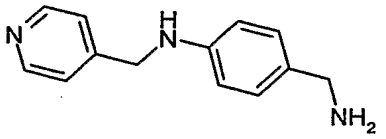
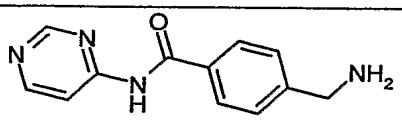
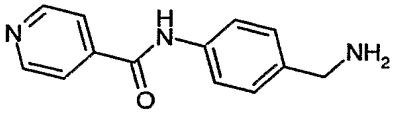
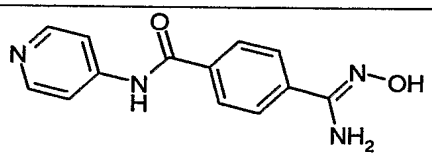
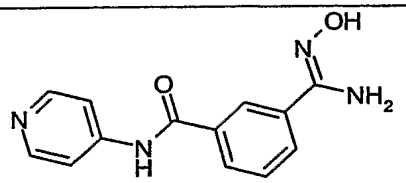
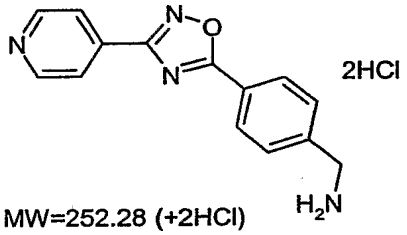
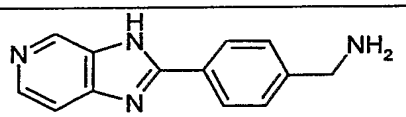
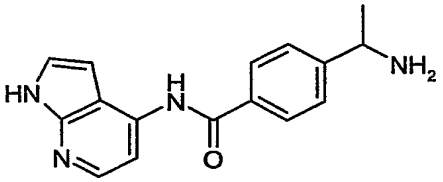
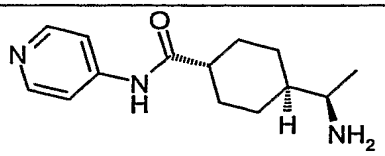
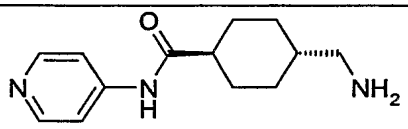
Ex	Formula	IC_{50} μM			
		PKCϵ	PKCγ	PKCθ	PKCζ
16	 3HCl MW=213.28 (+3HCl) D = 11.36	>100	>100	>100	>100
17	 2HCl MW=228.26 (+2HCl) D = 11.01	34.41	>100	87.18	>100
18	 2HCl MW=227.27 (+2HCl) D = 11.4 Angstrom2	70.74	>100	77.72	>100
19	 MW=256.27 D = 11.10	>100	>100	>100	>100

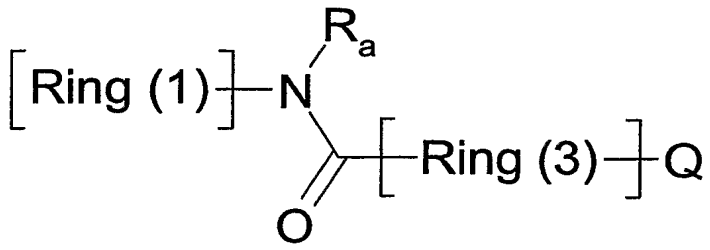
TABLE 1 (Continued)

Ex	Formula	IC_{50} μM			
		PKCε	PKCγ	PKCθ	PKCζ
20	 MW=256.27 D = 10.29	>100	>100	>100	>100
21	 2HCl MW=252.28 (+2HCl) D = 11.77	>100	>100	>100	>100
22	 MW=224.27 D = 10.52	>100	>100	>100	>100
23	 MW=280.33 D = 11.21	0.40	11.29	0.77	> 100

Ex	Formula	IC_{50} μM			
		PKCϵ	PKCγ	PKCθ	PKCζ
24	 2HCl MW=247.34 (+2HCl) Y-27632 dihydrochloride D = 11.12	1.74	>100	1.73	37.68
25	 MW =233.32 D = 11.16	5.12	> 100	7.35	24.33

CLAIMS

1. Compounds of Formula I:



(I)

in which:

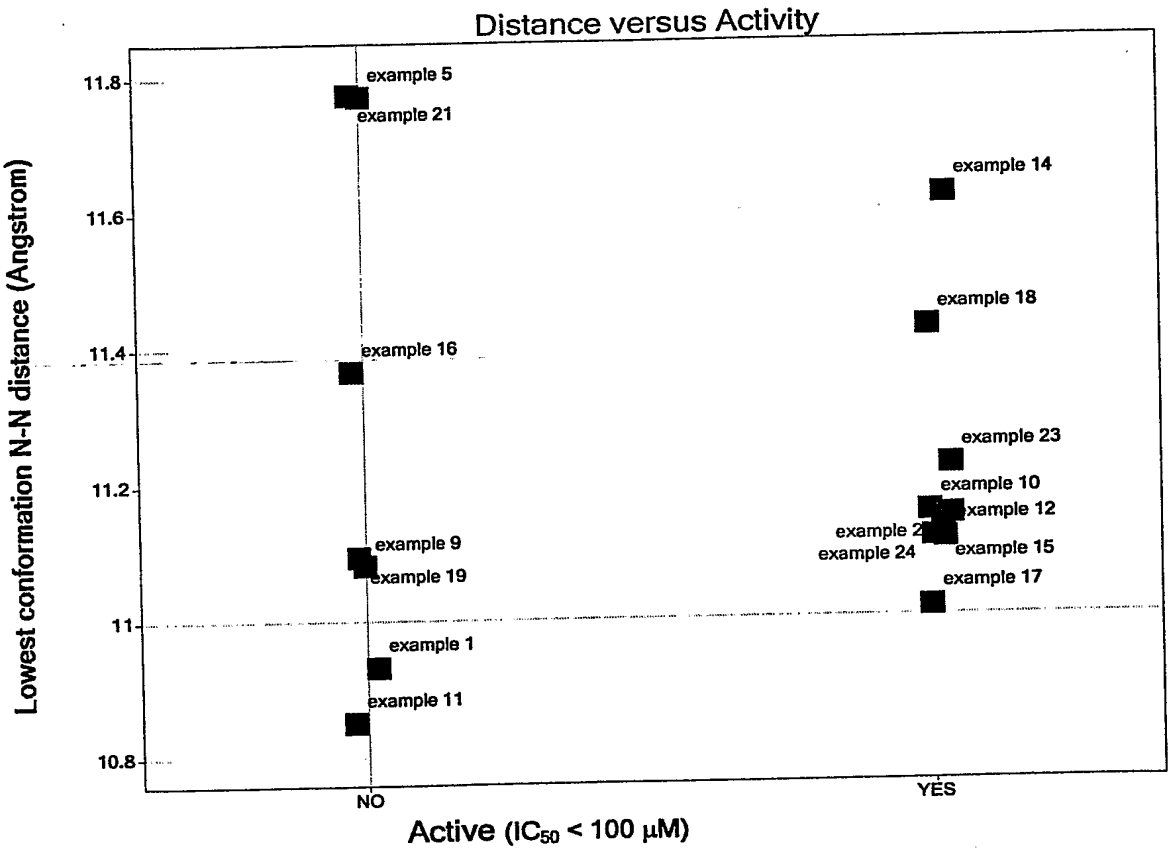
- Ring (1) is a substituted or unsubstituted, saturated, unsaturated or aromatic 4-, 5-, 6-, 7- or 8-membered ring containing carbon atoms and at least one hydrogen-accepting hetero-atom and optionally 1 or 2 further hetero-atoms;
- R_a is hydrogen, a linear or branched, substituted or unsubstituted C_1-C_6 alkyl, substituted or unsubstituted C_1-C_6 alkoxy or substituted or unsubstituted aryl; on in which R_a, the nitrogen atom to which it is bound, the carbon atom of Ring (1) to which said nitrogen atom is bound, and one carbon atom of Ring (1) adjacent to the carbon atom of Ring (1) to which said nitrogen atom is bound, may form a substituted or unsubstituted, saturated, unsaturated or aromatic 4-, 5- or 6-membered ring that contains carbon atoms, said nitrogen atom and optionally one further heteroatom chosen from oxygen, sulfur and nitrogen;
- Ring (3) is a substituted or unsubstituted, saturated, unsaturated or aromatic 4-, 5-, 6-, 7- or 8-membered ring containing carbon atoms optionally 1 or 2 hetero-atoms;
- Q represents an alkylene aminogroup, in which said amino group is such that, at a pH of between 5.0 and 9.0, preferably between 6.0 and 8.0, such as about 7.0, it is essentially in a protonated form;
- the distance between the at least one hydrogen-accepting hetero atom in Ring (1) and the nitrogen atom of the amino group in the group Q, as determined using a

Scatter Plot (generated as indicated above), is in the range of 11.0 to 11.8, preferably 11.0 to 11.6, and more preferably 11.0 to 11.4 Angstrom.

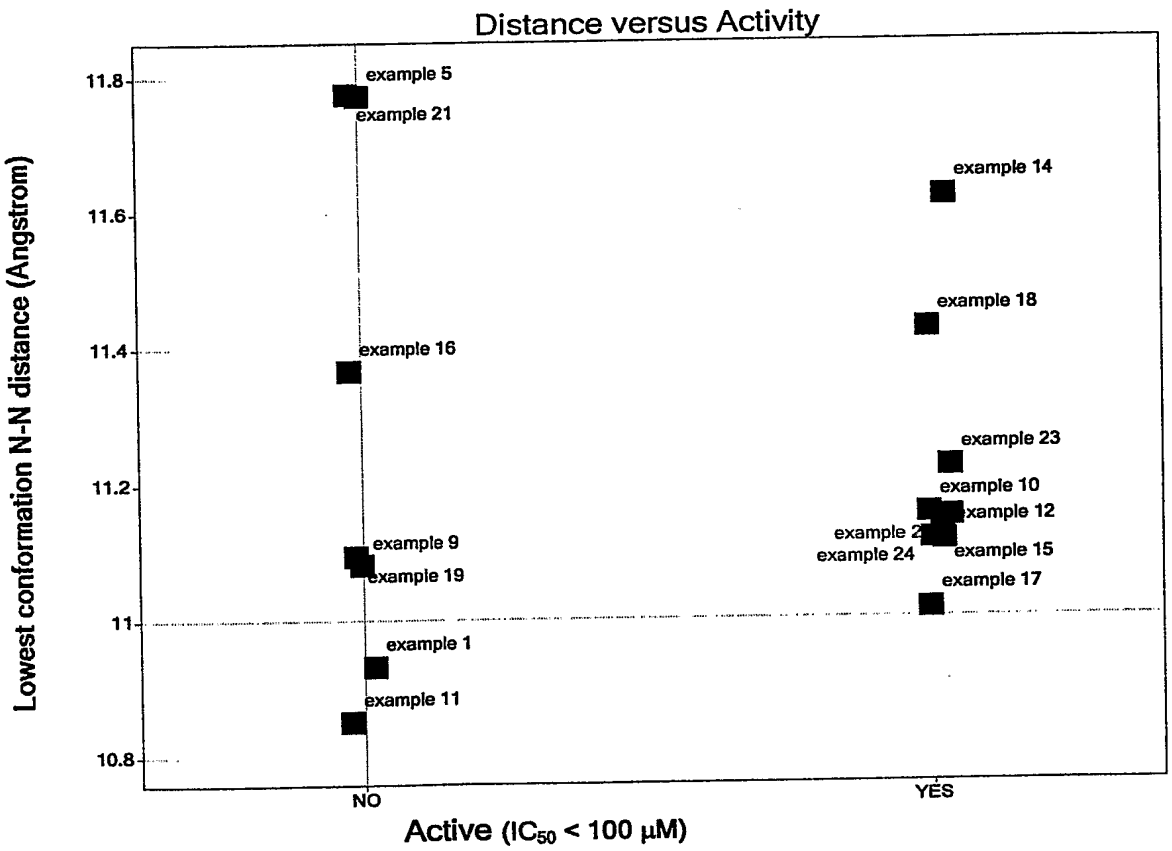
2. Compounds of Formula I, in which the hydrogen-accepting hetero-atom in Ring (1) is a nitrogen atom.

3. Pharmaceutical and/or veterinary composition containing a compound of claim 1 or claim 2.

Figure


Distance versus Activity
Lowest conformation N-N distance (Angstrom)
11.8
11.6
11.4
11.2
11
10.8
example 5
example 21
example 14
example 18
example 16
example 23
example 10
example 12
example 2
example 24
example 15
example 9
example 19
example 17
example 1
example 11
NO
YES
Active (IC50 < 100 µM)

Figure


Distance versus Activity
Lowest conformation N-N distance (Angstrom)
11.8
11.6
11.4
11.2
11
10.8
example 5
example 21
example 14
example 18
example 16
example 23
example 10
example 12
example 2
example 24
example 15
example 9
example 19
example 17
example 1
example 11
NO
YES
Active (IC50 < 100 µM)